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THE RELATIONSHIP OF ROUTINE PULMONARY FUNCTION STUDIES TO PULMONARY MECHANICS STUDIES IN OBSTRUCTIVE AIRWAY DISEASE

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE MASTER OF SCIENCE (MEDICINE)

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by

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APPROVAL SHEET

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Relationship of Routine Pulmonary Function Studies to Pulmonary Mechanics Studies in Obstructive Airway Disease", submitted by Patricia Lynne-Davies in partial fulfillment of the requirements for the Degree of Master of Science (Medicine).

ABSTRACT

Comparisons were made between measurements of lung volume and spirometry and estimates of pulmonary mechanics in 13 asthmatic and 11 emphysematous patients on a total of 35 occasions.

Lung volumes, forced expiratory volumes and maximum breathing capacity were measured in the routine pulmonary function laboratory of the University of Alberta Hospital. Subjects were then taken immediately to the mechanics laboratory where, using the oesophageal balloon technique, lung compliance and airway resistance were assessed. Work loops were constructed from the intra-oesophageal pressure and tidal volume tracings, and from these the elastic, resistive and total work of breathing measured.

Attempts were made to correlate the vital capacity, forced expiratory volume 1.0 second and maximum breathing capacity with various parameters of the mechanical function of the lung. It was found that in emphysema there was a highly significant negative correlation between the forced expiratory volume and expiratory airway resistance ($r = -0.98$, $p < .01$). A significant correlation also existed between FEV 1.0 and expiratory resistive work ($r = -0.68$, $p < .02$).

In asthmatic subjects the forced expiratory volume was related

to lung compliance ($r = 0.68$, $p < .02$) and to the sum of elastic and expiratory resistive work. ($r = -0.67$, $p < .01$). The vital capacity was also found to be related to the lung compliance ($r = 0.67$, $p < .01$).

Other attempts to determine any meaningful relationship between the vital capacity or maximum breathing capacity and the results of the various mechanics studies were unsuccessful.

It was concluded that ventilometry measurements and pulmonary mechanics studies are complementary investigations in subjects with chronic obstructive lung disease. It was further felt that asthma and emphysema represent two conditions, often similar in their clinical symptomatology, which nevertheless differ profoundly in the fundamental pathophysiology.

ACKNOWLEDGEMENT

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PREFACE

The apparent increase in the incidence of chronic obstructive lung disease during recent years has aroused considerable interest amongst physicians and clinical physiologists. Numerous investigations have been conducted to elucidate the pathophysiology of the various conditions characterized by airway obstruction, and to improve the accuracy of diagnostic techniques in clinical practice. Notwithstanding the considerable body of literature which has accumulated as a result, there have been only limited attempts to correlate routine spirometry findings with the figures derived from the more sophisticated studies of pulmonary mechanics. Since the latter attempt to measure the dynamics of lung function, presumably they should provide a better assessment of a subject's current status and prognosis; and it seems important to establish the extent of agreement between these dynamic measurements and the essentially static estimates obtained by ventilometry.

The present investigation was therefore designed to complement the results presently available in this field, and to explore further some of the apparent contradictions in previous reports, in an attempt to determine whether or not there is any correlation between spirometric findings and the results of pulmonary mechanics studies.

INTRODUCTION

Tests of pulmonary function are designed to assist the investigator in any or all of the following ways:

1. as an aid to the understanding of a disease process.
2. as an aid to the diagnosis of disease.
3. as a means of providing objective measurements of the progression of a pathological process.
4. as a means of evaluating therapeutic procedures.

The available tests fall into two broad classes: spirometry and studies of pulmonary mechanics. The first measures lung volume and its sub-divisions, together with certain time-volume relationships. The latter essay to measure various parameters of the elastic and resistive properties of the lungs, for the purpose of providing accurate information concerning the dynamics of pulmonary function. Of the two, spirometry offers the advantages of simplicity, economy and convenience to the patient and investigator alike. Mechanics studies, on the other hand, require instruments of considerable sophistication and expense, while the analysis of results is time consuming and laborious. Moreover the technique of recording pressures from an intra-oesophageal balloon causes the patient some minor discomfort, which further limits the clinical applicability of these methods. To

justify their use, therefore, it must clearly be established that they provide significant information which is otherwise unobtainable.

There is a considerable body of literature dealing with the measurement of lung compliance and with the work of breathing; but in only a limited number of cases has there been a considered attempt to correlate results obtained with the spirometric findings, nor are the conclusions reached by various investigators entirely in agreement.

Airway obstruction will manifest itself by reductions in the forced expiratory volume at a specified point in expiration (FEV 0.5, 1.0 or 2.0 secs.) and in the maximum breathing capacity (MBC).[49,108] These are frequently associated with a slightly reduced vital capacity (VC).[22,58] There is also an increased resistance to airflow during inspiration (Ri) and expiration (Re), generally associated with a reduced lung compliance (CL) and increased work of breathing.[5,67,68,107] Superficially it would seem reasonable that these changes should parallel each other, and indeed the assumption is often tacitly made. Available data, however, only partially confirm this supposition; and it remains open to doubt whether any measurements made during forced expiration provide a true index of airway resistance in asthmatic or emphysematous

patients, since all involve a most abnormal manoeuvre which is markedly different from the normal breathing pattern of expiring against pursed lips which is seen in these conditions.

REVIEW OF THE LITERATURE

a. Incidence of Obstructive Airway Disease:

The major disease entities characterized by airway obstruction are bronchial asthma and pulmonary emphysema (with which, according to North American usage, is classified chronic bronchitis).[37]

It is generally accepted that the incidence of major allergies including those with respiratory tract manifestations, is one in ten[84] while one person in 75 is clinically diagnosed as having asthma.[96]

The incidence of pulmonary emphysema is more difficult to ascertain, though there seems little doubt that it is increasing in frequency.[56] To what extent this apparent increase may be attributed to the greater awareness of physicians is uncertain. Attempts to determine the actual incidence of the bronchitis-emphysema syndrome in the population at large have varied from the epidemiological approach[2,32,48,51] to surveys undertaken at autopsy.[50,71,105] Amongst the former, Greene and Berkowitz estimated half the men and one fifth of the women in a

total of 4,322 patients requiring surgery for a wide variety of complaints had chronic cough.[48] Chronic bronchitis was diagnosed in 10.7% of older males surveyed in Leigh, England,[51] and in 21.2% of similar patients in Berlin, New Hampshire.[32] Moreover, as Anderson et al[2] have pointed out, the prevalence of respiratory disease will be underestimated if calculations are based upon studies of cooperative subjects who voluntarily attend a screening clinic. They found a significantly higher percentage of physiological abnormalities among those subjects who failed to attend such a clinic. In a number of post mortem surveys, severe emphysema has been found in approximately 6.5% of all autopsies.[105] However, cor pulmonale represented 40% of all admissions with congestive heart failure in Sheffield, England,[101] and 10% of such admissions in Denver, Colorado. In Britain chronic bronchitis now represents the third most common cause of death.[86] While chronic obstructive pulmonary disease is less common in North America, in the United States deaths reported as due to emphysema more than doubled in the period 1954 - 1959,[84] and in Oregon [83] deaths from emphysema increased about twelve fold between 1950 and 1961.

It is against this background of both increasing incidence and increasing awareness that the present study has been planned.

b. Relationship between vital capacity, lung compliance and airway resistance.

There have been a number of reports that there is a good correlation between CL and VC in normal subjects and in patients with cardiac disease.[13,38,39,75,97] Ebert[29] points out that CL must be related to the degree of lung inflation since the pressure-volume curve for the lung is not a straight line. Because of the generalized fragmentation of elastic tissue which occurs in emphysema,[108] the curve is shifted upwards while retaining a relatively normal shape, so that measurements of static compliance in this condition give values higher than normal. However it has been shown that in emphysema CL becomes flow-dependent, and therefore varies with the respiratory rate, probably because of the characteristically uneven ventilation.[12] As a result CL measured under dynamic conditions is found to be in the low normal range.[3,5,38] In view of this phenomenon most workers have reported a poor correlation between VC and CL in diseases such as emphysema or asthma, where there is abnormally high airflow resistance.[25,30,49,59,74,88]

While obstructive pulmonary disease is often associated with a reduced VC the relationship is not a direct one. In the view of most authors, therefore, VC is a poor index of airway obstruction[5,13,17] though Bartlet et al[8] found that VC was related to Re but not to Ri.

Attinger and his co-workers, in one of the few papers directed to the problem of correlating the various methods of assessing pulmonary function,[4] point out that mechanics studies reveal abnormalities at a time when routine tests are still within normal limits.

c. Relation of expiratory measurements to airway resistance.

Attempts have been made to investigate volume-time relationships during forced expiratory manoeuvres, either by means of the FEV[44] or the maximum mid-expiratory flow rate (MMEF).[59] Many investigators believe that such tests currently provide the best method of detecting ventilatory abnormalities associated with airway obstruction.[35,49] Rainer and his associates[90] found that the expiratory reduction in tracheal and major bronchial diameters, as measured by cinefluorography, closely paralleled the reduction in FEV 1.0 Ritchie[93] compared FEV measurements with peak expiratory flow and found a reasonable correlation, but noted that the spread of observations was such that the prediction of one value from the other was impracticable. Ebert[29] states that the reduced flow rate, FEV and MBC noted in emphysema is related in general to the increased airway resistance, without indicating any precise interrelationships.

There has been some debate as to which of these measurements most accurately reflects airway obstruction. Attinger and his co-workers[5] have claimed that the MBC is preferable to the FEV in this respect, since it measures both the inspiratory and expiratory phases of respiration, but admit that "only in the presence of increased resistance can a low MBC be interpreted as indicative of bronchial obstruction". This would seem to throw the onus of diagnosing abnormal resistance on the clinician, for Miller et al[81] have pointed out that an accurate assessment of the MBC depends on the patient's motivation, coordination, endurance and training, as well as a respiratory rate in excess of 65 per minute (so as to utilize the steepest part of the expiratory flow curve). In spite of this rather daunting list of possible variables, these workers found it was possible to estimate the MBC from the FEV 0.5, 1.0 or 2.0 secs. with essentially the same reliability. However Motley[82] found the FEV 1.0 a better guide of airway obstruction than FEV 3.0, and the MBC relatively more affected than either in emphysema. Nevertheless, since the MBC in some sense assesses a subject's muscular power as well as his intrinsic pulmonary function, Gaensler[44] considered it a poor test in patients who

were un-practised, weak or very sick. More specifically, he found that the MBC in asthmatic or emphysematous subjects underestimated the maximal exercise tolerance. This he attributed to the high intrapleural pressures associated with conscious forced expiration. These might be expected to exaggerate the ball-valving characteristic of these disorders.[25] That high intrathoracic pressures tend to be a self-perpetuating vicious circle has been noted by Dekker et al.[26] For all these reasons some workers prefer FEV[102] or peak expiratory flow measurements,[59] while Hall[49] has condemned the MBC in the following terms "the age for compulsory retirement would appear to have been reached for this old standby". There is some support for this view in the studies of Sweet et al[102] who found a poor correlation between the MBC measured ante mortem and the degree of emphysema demonstrated at autopsy.

However the basic conflict remains unresolved in the light of the most recently available reports. Lloyd and Wright,[61] studying ten normal subjects in whom bronchospasm and then relaxation were induced, found highly significant changes in the airway resistance as measured by the plethysmographic method which were mirrored by changes in the MBC and maximum mid-expiratory flow rate in about 70% of cases. They found the peak flow rate and FEV 1.0 to be minimally affected. In this study changes in a given parameter were considered significant if they exceeded certain pre-fixed percentage alterations, the value for each parameter

having been agreed upon following previous experimental observations. No statistical analysis of their results is offered. On the other hand Stein et al[100] after studying 27 patients with a clinical diagnosis of obstructive pulmonary disease, found a significant correlation between airway resistance and the FEV 1.0, maximal expiratory flow rate and maximal mid-expiratory flow rate ($p = 0.01$) but only a borderline correlation between resistance and MBC or peak flow rate.

Both these investigations employed the plethysmographic method of estimating airway resistance, in which measurements are made during panting respirations. The precise relationship between resistance to airflow under these conditions and resistance during a normal respiratory pattern remains unknown, but it seems evident that studies employing a rapid respiratory rate (sometimes in excess of 200 per minute[55]) in patients whose minute ventilation is already low, will lead to a grossly reduced tidal volume sufficient to effect little more than an exchange of the dead space air. Therefore any measurements obtained by such a method are likely to assess the physical characteristics of the major airways only. Nor did any of the studies which have been referred to include measurements of compliance or other parameters of mechanical function.

In summary, in the current literature a conflict of opinion still exists as to which of the routine measurements of pulmonary function

provides the best assessment of resistance to airflow. Attinger et al[4] and Lloyd and Wright[61] believe airway resistance is most accurately reflected by the MBC, whereas Stein and his co-workers[100] found the FEV 1.0 to be the more reliable estimate. There is support for the latter view in the work of Lefcoe.[57]

d. Correlation of spirometry and work of breathing.

Finally there have been few attempts to correlate measurements of the work of breathing with the results of routine pulmonary function studies, though Eldridge and Davis[30] have reported the former as a more satisfactory index of respiratory stimulation than measurements of external ventilation.

METHOD

Selection of Subjects.

All the patients involved in this investigation had a clinical diagnosis of obstructive lung disease. They were selected on the basis of history, clinical assessment, x-ray findings and the results of spirometry. Of these, the most reliable single aid in the diagnosis of airway obstruction is spirometry.[21,22,110]

Since it is reasonable to suppose that not all patients with airway obstruction will behave in an identical fashion (depending upon the extent of irreversible changes in lung architecture) the group was further sub-divided into those subjects who were primarily asthmatic and those who,

it was believed, had well-established emphysema. While the distinction may sometimes be difficult to make, in this context particular attention was paid to the potential reversibility of the obstructive defect by bronchodilators, to the degree of hyperinflation that was present, and particularly to the diffusing capacity. While the latter remains relatively normal in asthma, it becomes progressively reduced in emphysema, and provided that changes in lung volume are taken into account, will usually serve to distinguish between the two conditions.[9,36]

APPARATUS AND TECHNIQUE

Lung Volumes and Spirometry:

The Godart Pulmotest, Model 1.A.7000 was used. Since the aim of this investigation was to correlate the usual parameters of pulmonary function with the results of pulmonary mechanics studies, the former were measured by the currently employed techniques in the routine pulmonary function laboratory of the U. of A. Hospital. (Figure I).

Functional Residual Capacity:

This was determined by the closed circuit helium technique.[10,76] The patient was seated comfortably and allowed to adjust to the mouthpiece and spring nose-clip for at least five minutes. The measurement commenced at the end of a normal expiration, and readings were monitored constantly. The point of equilibrium was determined by obtaining three consecutive identical concentrations of helium, at 30 second intervals after a minimum period of eight minutes.

Figure I

Godart Pulmotest Model 1.A 7000

Expiratory Reserve Volume:

This was obtained by having the patient expire maximally after a normal expiration, and the test was repeated until reproducible values (within 50 ml.) were obtained, the largest value being recorded. This is customarily selected[79] in preference to the mean value because patients with airway obstruction easily become exhausted by repetitive manoeuvres of this nature and fail to reproduce their best efforts for reasons which may be due to their chronic debilitated state as much as their intrinsic pulmonary disease.

Residual Volume:

The residual volume was obtained by subtracting the expiratory reserve volume from the functional residual capacity.

Forced Vital Capacity and Forced Expiratory Volume 0.5 and 1.0 secs.:

These were measured by having the patient take a maximal inspiration followed immediately by a maximal forced expiration. The total volume expired was the forced vital capacity (FVC). The test was repeated until reproducible values (within 50 ml) were obtained, and the largest value recorded. The volumes obtained in the first half and one second respectively were the forced expiratory volumes (FEV 0.5, FEV 1.0). Here too reproducibility within 50 ml. was required, and the largest volumes were recorded.

Maximum Breathing Capacity:

This was measured by having the patient breathe maximally for 15 secs.[19:202] and multiplying the value so obtained by four to give the minute volume.

Normal Values:

The values of Baldwin, Cournand and Richards[6] were used, since these are routinely employed in the Cardiopulmonary Laboratory of the University of Alberta Hospital. (These predictions were found to agree with figures obtained in this laboratory from studies of ten normal young adults of either sex: see page 32). All gas volumes were measured at ambient temperature and pressure, saturated with water vapour (ATPS), and converted to body temperature and pressure saturated with water vapour (BTPS).

MECHANICS OF BREATHING

The apparatus used consisted of the Godart Pneumotachograph with volume integrator, type GM-0577, a latex oesophageal balloon with attached polyethylene catheter and an Electronics for Medicine Oscilloscope recorder, type DR-8.

Godart Pneumotachograph with Volume Integrator: (Figure II)

The Godart Pneumotachograph is a device used to record instantaneous airflow to and from the lungs. The flow rates are then integrated electronically to provide a simultaneous record of the respiratory volumes.

The patient breathes into a flow-transducer, across the center of

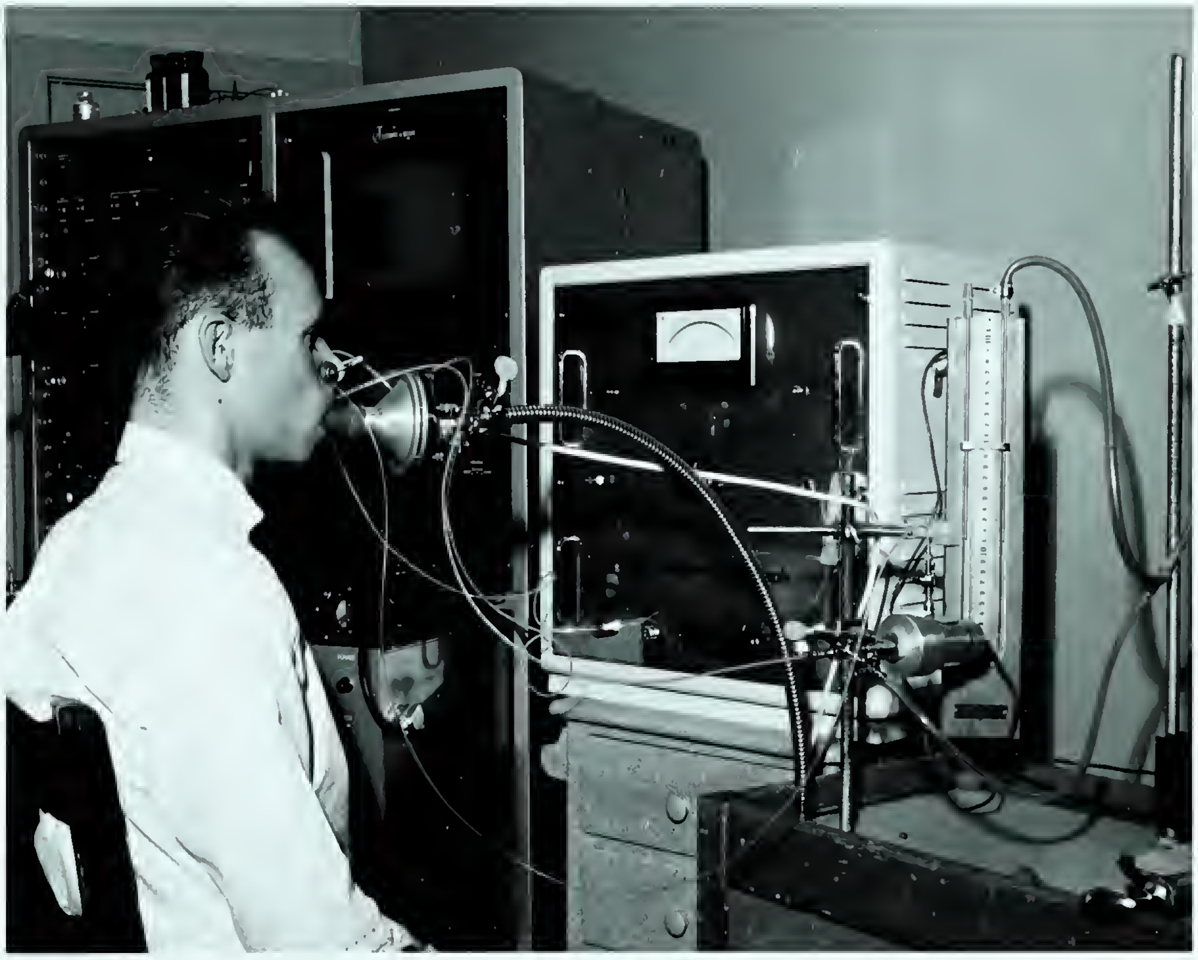

Figure II

Godart Pneumotachograph

which is stretched a wire gauze membrane. When gas flow occurs, a pressure difference is set up across this membrane, giving rise to a signal which is fed into a pressure receptor with transducer. The pressure gradient is thus transmitted to either side of a metal diaphragm, movements of which are sensed by a metal probe suspended within two coils. The inductance changes due to movements of the metal core are measured and give rise to an electrical signal. This is then amplified in three stages with negative feedback and detected by a phase sensitive rectifier, the resultant flow tracing being transcribed by the recorder.

The signal is also fed into a galvanometer provided with a scale calibrated in litres per minute on the front panel of the apparatus, and from here to the volume integrator, which contains a D.C. amplifier. In the feedback of this amplifier there is an R.C. filter with sufficiently long R.C. time. In this way the changing signal for rate of flow is registered, integrated and displayed as a static level, indicating the total volume of gas passed to and from the lungs.

For the purposes of this investigation the pneumotachograph was calibrated with the Godart Flowmeter, type 121, at the beginning of the experimental procedures and again at their conclusion. On both occasions it was found to be linear for flow rates up to 130 litres per minute, which was adequate for the present study.

The wire gause screen requires meticulous cleansing after every study, as accumulation of mucous will seriously affect the results obtained. The screen was washed regularly in alcohol, and dried carefully before use. It was heated to 38 C on each occasion, using the electrical heating coil provided with the instrument. The air to be inspired was thus warmed to body temperature, which tended to reduce the difference between inspired and expired volume.

The volume-integration switch was used at "Position 2", whereby each inspiration and expiration is integrated separately. The type of tracing so obtained, on which are superimposed time lines at 0.04 sec. intervals, is ideal for the construction of accurate work loops.

Oesophageal Balloon and Catheter:

The oesophageal balloons were constructed by the staff of the Inhalation Therapy Department, University of Alberta Hospital, after the pattern of original models supplied by Dr. J. Milic-Emili of the Department of Physiology, Harvard School of Public Health.[79] The balloon is made of very thin latex and measures 10 cm. in length and 3.5 cm. in circumference. The balloon is sealed to a polyethylene catheter of internal diameter 1 mm. with Pliobond adhesive. Small holes are present in the portion of the catheter lying inside the balloon, arranged spirally at intervals of 0.5 cm. The distal end of the catheter is sealed and the tip of the balloon strengthened with Pliobond adhesive. Although these balloons are

fragile, with careful handling they can be used on many occasions. Following use the balloons are dried carefully, and maintained in the inflated position to prevent the walls from adhering. It is essential to prevent any droplet of water from entering the tubing, as even the smallest quantities may produce a markedly distorted pressure tracing.

The balloon was lubricated with 'MUKO' (a water-soluble substance) and passed into the subject's oesophagus via the nostril. It has been shown experimentally[78] that pressure readings obtained from the upper third of the oesophagus are subject to errors related to changes in mouth pressure, head posture and external pressure on the trachea; while readings obtained from the lower one-third vary markedly from point to point and also with body posture. The balloon was therefore introduced into the mid third of the oesophagus. The normal distance from the external nares to the junction of the middle and lower thirds of the oesophagus is normally 37 - 43 cm., and using this as a rough guide the exact position which provided maximum pressure amplitudes for each subject was determined. The precise distance was carefully recorded, and the balloon re-inserted in this position if studies were repeated at a later date.

The balloon was inserted in a flaccid state, and the free end of the catheter attached to a three-way stopcock which had opening to the atmosphere and to a Statham differential pressure strain gauge transducer. A syringe with an easily gliding plunger was attached to the atmosphere

opening of the stopcock, and the balloon emptied by the patient performing several Valsalva manoeuvres. 5 mls of air were then introduced into the balloon and recovered by the subject performing further Valsalva manoeuvres. Finally 0.2 ml. air was introduced into the balloon, and the system connected to the strain gauge transducer. There are several reasons for this procedure. Firstly, the complete emptying of the balloon by suction with a syringe is inadvisable as this may induce adherence and creasing of the walls of the balloon. The introduction of 5 ml air when the balloon is in place serves to spread the surface of the balloon evenly to the oesophageal wall, as the balloon may have been twisted on its introduction in the flaccid state. Finally this volume is replaced with 0.2 ml. air which has been found to give realistic and reproducible values with this type of balloon.

The pressure system was calibrated using a water manometer prior to each study.

<u>Electronics for Medicine Oscilloscope Recorder Type DR-8</u>:

Its wide range of paper speeds (5 - 200 mm. per second) and time lines (0.004 - 1.0 sec.) make this recorder particularly suitable for the analysis of pressure-volume-flow relationships.

One of the main disadvantages of the use of the oesophageal balloon technique for accurate work is the fact that the heart beat is superimposed to a greater or lesser extent on the oesophageal pressure tracing. By having the subject breathe at a rapid rate, it is possible

to obtain a smooth and more regular tracing.

The sensitivity of the recorder was set so that 1 mm of volume deflection represented 15-30 ml., 1 mm. of pressure deflection represented 0.2 - 0.3 cm. water, and 1 mm. of flow deflection represented 1.5 - 2 litres per minute. In each case the precise values were determined immediately before readings were made.

PROCEDURE

Patients were usually studied in the morning, and always at least one and a half hours following their previous meal. Where repeat studies were obtained, these were made at the same time of day as the original readings.

Measurements of the lung volume and its subdivisions were performed in the Routine Pulmonary Function Laboratory using the Godart Pulmotest, as already described. Each patient was seated comfortably in the erect position. When these measurements had been made, the subject was immediately taken to the Mechanics Laboratory. There the oesophageal balloon was introduced. When the balloon had been positioned correctly and a satisfactory pressure tracing obtained, the patient rested while the remainder of the procedure was carefully explained. Particular emphysis was laid on the desirability of maintaining a constant respiratory rate (usually 40 - 45 breaths per minute, at which rate pressure fluctuations from the cardiac impulse are for the most part smoothed out) and a

constant tidal volume. A metronome was employed as an aid to the former, though it was often found that the subject's ready cooperation could be obtained if the investigator breathed audibly at the required rate. Thereafter patients apparently experienced little difficulty in maintaining a constant respiratory rate and volume. The patient was given no indication of the tidal volume he was expected to achieve, and while studies in normal subjects have usually aimed at volumes of 450-600 ml., the tidal volume in obstructed individuals is frequently lower (in the region of 300 ml). The only requirement was that the subject should select a breathing pattern which he could maintain without discomfort for approximately two minutes.

The oesophageal balloon was secured in position with adhesive tape and a spring nose clip, and the patient was attached to the mouth-piece of the pneumotachograph. Care was taken to ensure that he was seated in an erect position, and when he felt comfortable and accustomed to the mouth-piece, recording was commenced. With the subject breathing at a constant rate and volume in the manner specified above, simultaneous tracings of pressure, flow and volume over a period of 2 - 3 minutes were obtained.

It had originally been planned that at the conclusion of this part of the procedure, the subject's FRC would again be checked using a volume displacement body plethysmograph. Equipment breakdown prevented

this from being measured in all cases. However available measurements confirmed previous experimental findings in this laboratory, that the FRC showed no significant change during the relatively short time during which all the readings were obtained.[79,80]

ANALYSIS OF RECORDS

Theory:

Pulmonary mechanics studies are concerned with the measurement and inter-action of three variables: volume, flow and pressure. Pressure, in this contest, requires more precise definition. In effect, it represents the "driving pressure" of the lung system[19] and is represented by the transpulmonary pressure (TPP): that is, the gradient between the pressure acting on the lung surface (intra-pleural pressure) and the outlet pressure which is atmospheric. The intrapleural pressure is itself the product of complex forces. During moments of no-flow, when lung volume is constant, it represents a balance between the elastic recoil of the lungs, acting inwards, and the elastic recoil of the tissue of the chest wall acting in the opposite direction. As the respiratory cycle progresses, there are superimposed on these various muscular and resistive forces,[46] the sum of which at any one moment represents the intra-pleural pressure.

The pressure so developed must be employed to overcome three factors: the elastic recoil of the lungs, the frictional resistance to flow in the air passages, and the resistance to deformation of the lung

tissues. Of these, the lung tissue resistance represents a negligible part of the total resistive work[19:190] (in normal individuals less than one-sixth of the whole[64] and only slightly more in emphysematous subjects[65]); and since its measurement is technically difficult, it is customary to consider airway resistance and lung tissue resistance together under the heading of resistive work[79] although such a concept is not strictly accurate. Thus the work of breathing can be subdivided into elastic work which becomes stored as potential energy during inspiration, most of which becomes available to the body again during expiration, and resistive work which, owing to friction, becomes dissipated as heat. Of these, the former is proportional to the degree of distension of the lungs (specifically, to the square of the tidal volume),[85] while the latter is a function of air flow.

This subdivision of work of breathing into its elastic and resistive components was clearly delineated by Rohrer in 1925, [95] whose findings and deductions were later confirmed by Von Neergard and Wirz.[85] However the implications of their work were not further explored until the work of Rahn.[89] One of the reasons for this was the difficulty in measuring the intrapleural pressure in human subjects. Further progress came with the realization that intraoesophageal pressure, while not equal to intrapleural pressure, is an adequate representation of it.[16,18,27,41,72,73,98]

This is because the oesophagus is an organ of rather low intrinsic tone which, like the pleural space, lies inside the thoracic cage but outside the lungs. More recent work[23] has confirmed the earlier findings, and demonstrated that intrapleural pressure itself varies at different points on the lung surface, while it has also been shown that both intrapleural and intraoesophageal pressures agree well with bronchiolar "wedge" pressure.[106]

From the measurements of volume, flow and pressure it is possible to calculate lung compliance (CL), airway resistance during inspiration (Ri) and expiration (Re) and the total work of breathing, including elastic and resistive work.

Lung Compliance:

This, a measure of the "stiffness" of the lungs, represents the volume change obtained per unit pressure change, and is measured in litres per cm. of water pressure. It is therefore a reciprocal of lung elastance, a term which is no longer in common use.[19] Since it is an indication of the elastic, or static, properties of the lungs, it is measured at a moment of no-flow: that is, at peak inspiration. The value so obtained has been termed dynamic compliance, to distinguish it from static compliance which is determined only after the pressure-volume relationship in the lungs has had time to achieve an equilibrium. Normal values for dynamic compliance are 0.2 L/cm.H_2O. However it must be noted that compliance is related to the lung volume and therefore it is the ratio CL/FRC which in normal subjects is a constant.[19:174,20,60]

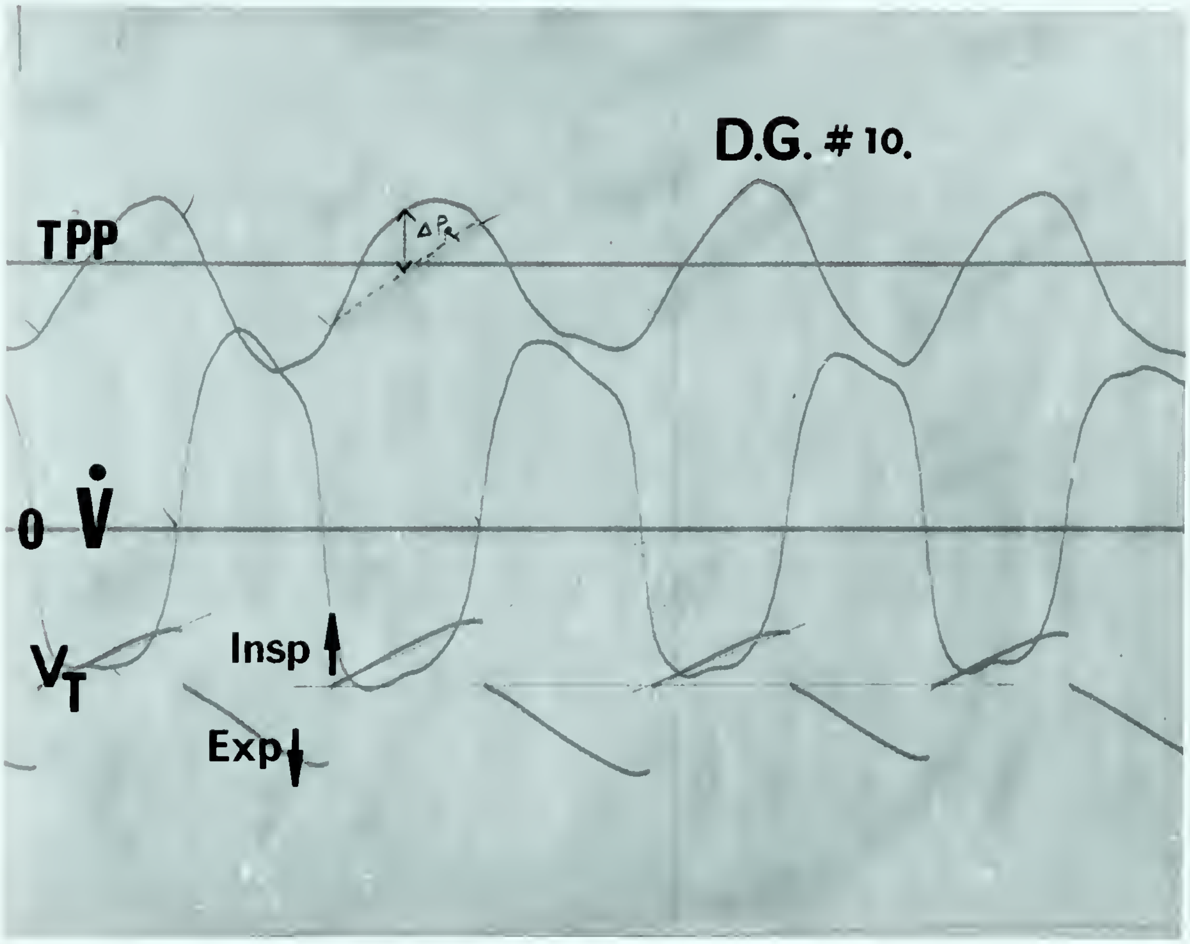

Figure III

Specimen record showing esophageal pressure, flow and volume tracing.

Airway Resistance:

The calculation of this factor depends upon the basic principle that the pressure required to overcome the elastic resistance of the lungs follows precisely the volume change.[31] (Figure III) Therefore, having regard to any change in scale, the shape of the volume curve may be superimposed on the pressure tracing. When this has been done, the residual pressure divided by the flow rate represents the resistance at that moment in the respiratory cycle. Resistance is expressed as cm.H_2O/L/sec. and normal values range from 1.8 - 3.4.[19]

Work of Breathing:

Measurements of the work of breathing were made from the trans-pulmonary pressure and tidal volume records, as described by McIlroy, Marshall and Christie.[69] The resultant pressure-volume diagram is shown diagramatically in Figure IV. Work is defined as the product of force and distance or pressure and volume. In the pulmonary system the appropriate variables are trans-pulmonary pressure and volume. Thus in the diagram the total work per breath is equivalent to the area ABCDEF, where the line AC represents lung compliance, and the triangle ACD the elastic work performed to distend the lungs. However during inspiration the actual plot follows the line ABC, so that the area ABCA represents inspiratory flow resistive work. The first part of expiration, CE, is seen to lie within the elastic work triangle: the previously conserved potential energy

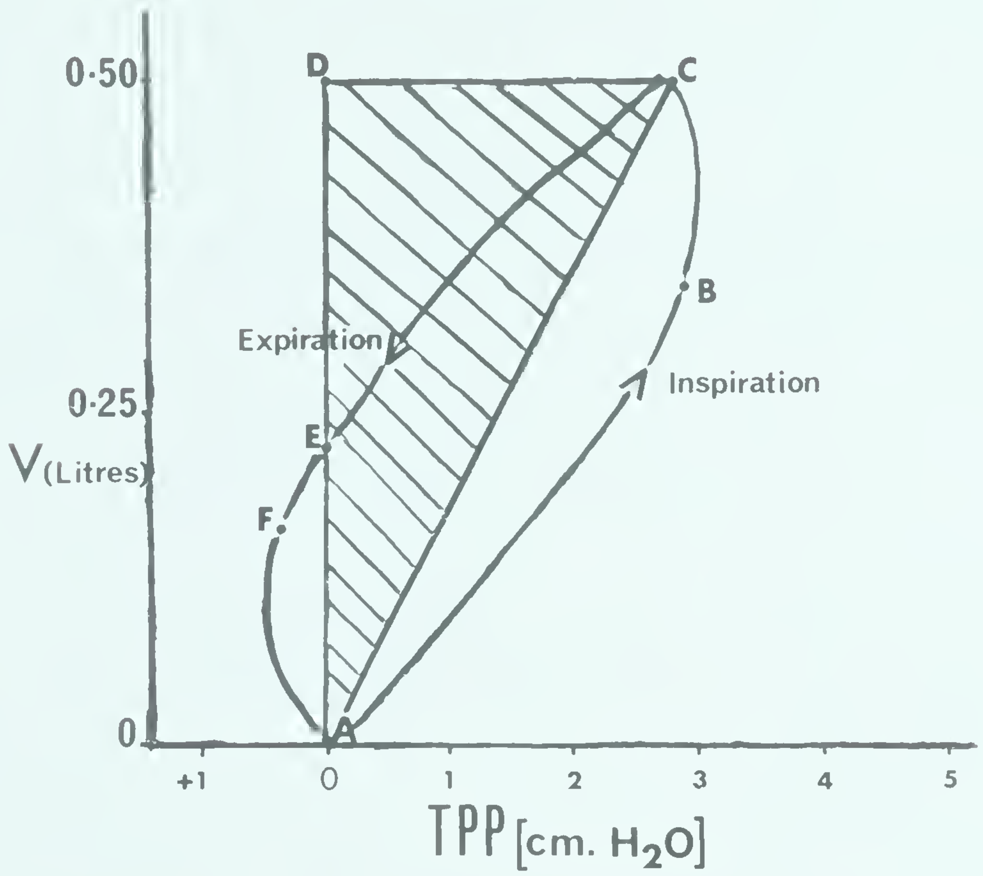

Figure IV

Diagram of Work Loop

becomes available, and the process is a passive one. The only active respiratory work, additional resistive work, is represented by the area EFAE. It follows that as expiratory airway resistance increases, this segment will become larger. Similarly in subjects with a low compliance, the work loop becomes flatter and also of larger area. The remaining area, CDE, which lies outside the actual work loop, represents a percentage of elastic work which is lost by reason of muscular resistance.[1, 12:364, 46]

Some Limiting Factors:

During the past twenty years a great deal of information has been accumulated regarding values for lung compliance, airway resistance and the work of breathing in normal subjects as well as for patients with a wide variety of pathological conditions. In spite of this, pulmonary mechanics measurements have achieved only a limited acceptance as diagnostic tools in clinical medicine. While this is unfortunate, for they can make a valuable contribution to our understanding of the pathophysiology of pulmonary disease, there are a number of both theoretical and practical reasons for their apparent neglect. In the past there has been a wide variation in normal values as determined in different laboratories, though this can easily be accounted for on the basis of differences in technique and early failures to appreciate the possible pitfalls in the recording of oesophageal pressure. Then it must be remembered that measurements of airway resistance represent an instantaneous estimate of a factor which will vary throughout the respiratory cycle according to

fluctuations in flow and volume.[1:457] That CL and airway resistance represent ratios only (and that spurious near-normal values may occasionally be obtained by varying both numerator and denominator in the same direction) is sometimes forgotten in the false security implied by measurements carried to two or three decimal places. Among the practical difficulties which have already been alluded to are the problems of expensive equipment which is available only in the larger centres; the relative inconvenience to the subject of the oesophageal balloon technique, which makes it difficult if not impossible to obtain readings from acutely sick patients; and the scrupulous care regarding balloon size, volume and position, as well as the subject's posture, which is necessary to ensure accurate pressure tracings.

ANALYSIS OF RESULTS

At the conclusion of the experimental studies, for each subject values were available for the lung volume with its subdivisions, the forced expiratory volume and the maximum breathing capacity, as well as for lung compliance, airway resistance during inspiration and expiration, and the total work of breathing including its elastic and resistive fractions. These raw data for the asthmatic and emphysematous subjects are presented in Tables I-VII inclusive.

It was the main purpose of the investigation to attempt to determine whether or not a significant correlation existed between any of the

spirometric values and the various measurements of pulmonary mechanics. As a secondary aim the values were studied in the hope of noting any suggestive trends which might cast light upon the function of the pulmonary system, or increase our understanding of the pathophysiology of asthma and emphysema. The available results were therefore scrutinised, bearing in mind the following principles:

i. On theoretical grounds compliance, as an index of the volume-pressure relationships in the lungs, may be expected to correlate with any measurement which reflects abnormal volume exchange.

ii. Resistance is the ratio, at any given moment, of pressure to flow rate. It should therefore bear some relationship to those parameters which assess volume time relationships in the lungs: that is, forced expiratory volume, and, since the maximum ventilation of the lung is limited by the rate of air flow, also maximum breathing capacity.

iii. Work, as the product of volume and pressure, will reflect abnormalities in the pressure requirements necessary to provide adequate volume exchange in the time available for each phase of respiration. Secondarily it seems reasonable that the total work performed may impose limits upon the maximum ventilatory capacity of the lungs.

A problem arises concerning the units in which the values to be compared are expressed. While it is generally desirable for all results to be expressed in absolute units (e.g. litres, or litres per second) it is also necessary to compensate for differences in lung volume in order to reach any meaningful conclusions where patients of different age, sex, body size and muscular developement are being studied. It has also to be remembered that the results of many tests available to the clinician are commonly expressed as percentages of a predicted normal value for the patient in question. Since pressure, flow and volume are so closely inter-related in the pulmonary system, if mechanics and spirometry results are to be compared it is necessary to make an adjustment on one side or the other to allow for differences in the volume at which the subject's lungs are functioning, as the pressure-volume relationship is alinear.[19,29] When compliance is considered this compensation can most easily be effected by relating compliance to volume (in this case FRC, since dynamic compliance was measured) for it has long been appreciated that it is the ratio CL/FRC which in normal subjects is constant.[19,29]

Flow is also related to lung volume, but in this case the necessary adjustment may more easily be made to the spirometric value. In considering values for FEV 1.0 it is possible to take either the absolute value in litres (which, as has been indicated, is relatively meaningless in comparing different subjects) or a percentage of a

predicted normal value, or a percentage of the subject's actual vital capacity. In this study the last value has been selected for use in the analysis of results, partly because this is the common clinical standard and also because it will be impossible for a subject to attain flow rates in excess of the limit imposed by the functional lung volume.

Measurements of the maximum breathing capacity have been adjusted, to percentages of the predicted normal value. In the University of Alberta Hospital Laboratory, as in many others[99] the normal values of Baldwin, Cournand and Richards[6] are employed for this purpose, the normal range for which is taken as 80 - 120%. To assess the accuracy of these predictions, ten normal young adults of either sex were studied and found to achieve MBC's averaging 111% predicted value (range 86 - 132%). Since the highest individual measurements obtained were on athletes in good training, it was felt that the agreement was sufficiently close for the present purpose. It is a subjective impression that in older patients the agreement is even closer.

In analyzing the results obtained, particular attention was paid to the following paired values:

1. <u>Vital capacity and Lung Compliance</u>:

It has previously been shown that a good correlation exists between these parameters in normal subjects.[39,75] This is apparently not true of patients with airway obstruction[3,5,25,38,74] especially

when the so-called dynamic compliance has been estimated, for in these cases the increased resistance to air flow in the tracheo-bronchial tree precludes adequate filling of all parts of the lung within the time available under the conditions of the test. Further, this increased resistance is often associated with an increase in the FRC which, as it has already been pointed out, will itself produce alterations in the compliance even in normal subjects.[19,60] In this study it was the ratio CL/FRC which was selected for comparison with the vital capacity (FRC and VC both being expressed in litres).

2. Vital Capacity and Elastic Work:

The elastic work of breathing is proportional to lung volume, specifically to the square of the tidal volume.[85] Normally it is to be expected that when the respiratory rate is fixed (as it was during the present study) the tidal volume will in turn bear some relationship to the vital capacity. On first consideration it seems unlikely that this will still hold true for conditions such as emphysema, where hyperinflation and an actual increase in vital capacity may be associated with a reduced tidal volume. One might therefore look for a possible difference in behaviour here between the severe asthmatic and emphysematous patients and the milder asthmatic group.

3. Vital Capacity and Resistive Work:

Resistive work is a measure of the frictional resistance to

airflow in the tracheo-bronchial tree, and airflow during expiration is itself proportional to lung volume. The possibility therefore exists of a relationship between vital capacity and resistive work.

In comparing these values VC was expressed in litres, and the various components of work of breathing as kilogram-centimetres.

4. Forced Expiratory Volume and Expiratory Resistance:

Superficially there is every reason to expect that these values, each of which directly reflects abnormalities in the flow rate, will show a good correlation. There is some disagreement, however, in previous reports; for while Stein et al[100] found an excellent correlation between the two parameters in a group of patients with obstructive lung disease, Lloyd and Wright[61] found the FEV 1.0 only minimally affected when they employed broncho-constrictor substances to induce marked increases in Re in a series of normal subjects. In a recent article Lefcoe[57] attempted to correlate expiratory resistance expressed as its reciprocal, conductance, with the FEV 1.0 in a motley assortment of patients, some of whom had normal lung function and some with unspecified types of pulmonary disease. The correlation coefficient for his group was 0.57, a figure of debatable significance.

The question arises as to which time derivative of the forced expiratory volume should be selected for comparison with Re. As the

ratio of pressure to flow, resistance will of course vary throughout expiration.[1:457] According to the method employed in the present study measurements are customarily made at or near mid-expiration, which suggests that FEV 0.5 secs. might be a more nearly comparable value. The reason for selecting instead FEV 1.0 arises out of the work of Fry and Hyatt, who constructed flow-volume curves for normal subjects and for patients with airway obstruction.[42,54] They found the first part of the curve to be effort-dependent, while the α -B section (which represents the flow-volume relationship during mid-expiration) remained fairly constant between different normal subjects. They therefore believe that the α -B segment of the curve is determined entirely by the properties of the lung parenchyma, respired gas and intrathoracic airways.[40,43] There is considerable support for their work[14,24,53] which agrees with the subjective impression obtained in the laboratory that the volume measured for the FEV 0.5 secs. may be influenced by the degree of the subject's cooperation.

In this investigation, therefore, a comparison has been made between the FEV 1.0, expressed as a percentage of the subject's actual vital capacity, and the expiratory resistance expressed in cm. H_2O/L/sec.

5. Forced Expiratory Volume and Resistive Work:

Again it seems eminently reasonable to seek a correlation between these two parameters, each of which in some way measures airway obstruction. However it must be questioned to what extent measurements

of airway resistance made during a relatively normal albeit rapid breathing pattern can be related to FEV values which are obtained while the subject performs a forced expiratory manoeuvre. It is recognized that the latter, by encouraging the development of high intrapleural pressures with a resultant increase in ball-valving, may give the equivalent of falsely high resistances.[1:458]

The further question arises as to which value for FEV should be selected for comparison with the expiratory resistive work (which, of course, represents the sum of airway resistance throughout expiration). Though there appear to be no previous studies which are immediately relevent to this point, the concensus of opinion seems to be that the FEV 1.0 is the most suitable value for predicting the MBC. For this reason it has been employed in the present study.

6. Maximum Breathing Capacity and Mean Airway Resistance:

In the past it has been argued that the MBC is superior to the FEV 1.0 as an index of airway obstruction inasmuch as it assesses changes which occur during inspiration as well as expiration.[5] There is some support for this contention in the work of Lloyd and Wright[61] who found that when they induced changes in airway resistance artificially, these were reflected by changes in the MBC in 70% of cases. However Stein et al, in a series which has been reported in summary only thus far, but may well have been subjected to more careful analysis, found a

correlation between these two parameters which was of only borderline significance.[100] This would agree with Lefcoe's series[57] in which conductance was compared with the MBC; here the coefficient of correlation yielded a value of 0.59. Only a percentage of the subjects he studied, however, were suffering from obstructive airway disease. It may be noted here that he also confirmed previous reports that the FEV 1.0 agreed well with the MBC.

In the present studies, as already indicated, MBC was expressed as a percentage of the predicted normal value for the subject, while mean airway resistance is represented by the fraction $\frac{Ri + Re}{2}$, expressed in cm.H_2O/L/sec.

7. Maximum Breathing Capacity and Resistive Work:

It has already been pointed out that, assuming the patient is otherwise in reasonable health and fully cooperative, the maximum minute ventilation will be limited by the maximal flow rate which can be achieved by the subject. This is confirmed by the good correlation which previous investigators have reported between the forced expiratory volume and the maximum breathing capacity.[57] It therefore seems reasonable to seek a possible relationship between the MBC and resistive work, as another expression of airflow. The major problem inherent in any such comparison involving the MBC revolves around the question of whether the measured volume truly represents the patient's maximal effort. The reasons for

this have been previously outlined in the relevant section of the review of the literature.

8. Maximum Breathing Capacity and Total Work:

Granted the many practical difficulties involved in obtaining a true value for the MBC, the figure measured by this manoeuvre represents the maximal ventilation of which the subject is capable. Likewise the total work for a given breath is a measure of the effort required of the patient. Where this is increased, as in asthma or emphysema, the additional work represents the resultant of all the factors limiting ventilation. It may therefore be expected to correlate with the MBC.

While this account represents an outline of the reasoning which suggests that meaningful inter-relationships may exist between certain of the values measured during the present investigation, it does not imply that examination of the results was limited by these considerations. Analysis of the results was extended to include any further paired values whenever developments suggested the possibility of a relationship.

The first step in considering the paired results was to plot one value against the other in each case. The graphs so constructed are presented in Figures V - XIV. Where there seemed to be any possibility of a significant relationship, standard deviations were calculated in the usual way,[7] and the coefficient of correlation determined. This, with the standard error for the number of cases in question, in turn gave the p value.

TABLE I SUBJECTS STUDIED

a) ASTHMA

SUBJECT	SEX	AGE yrs.	HEIGHT ins.	WEIGHT lbs.
1.	F	45	61.5	174
2.	M	67	66	146
3.	F	47	65.5	150
4.	F	38	63	107
5.	M	36	66.5	120
6.	M	61	71	169
7.	M	45	70	210
8.	M			
9.	F	40	61	160
10.	M	51	66	185
11.	M	32	73.5	134
12.	F	12	50.5	58
13.	M	48	64	162
Mean		44.5	64.7	151.4

TABLE I SUBJECTS STUDIED

b) EMPHYSEMA

SUBJECT	SEX	AGE yrs.	HEIGHT ins.	WEIGHT lbs.
1.	M	59	65	140
2.	M	59	71	121
3.	M	74	66.5	132.5
4.	M	66	70	145
5.	M	73	68	128
6.	M	41	65.5	144
7.	M	55	75	152
8.	M	69	72	130
9.	M	56	71	110
10.	M	65	68	130
11.	F	47	63	106
Mean		60.4	68.6	130.8

TABLE II LUNG VOLUMES

a) ASTHMA

SUBJECT	VC		TLC		RV		FRC	
	L	% Predicted	L	% Predicted	L	% TLC	L	% TLC
1.	2.72	88	4.28	104	1.56	36	2.23	52
2. a)	3.83	104	5.51	104	1.68	30	2.28	42
b)	3.55	96	5.69	107	2.14	38	2.50	44
3. a)	3.35	91	6.16	126	2.81	46	3.58	64
b)	3.46	94	5.94	121	2.48	42	3.54	60
4. a)	2.87	78	4.40	90	1.53	35	2.34	53
b)	2.90	79	4.50	92	1.60	36	2.56	57
5. a)	3.59	79	6.72	113	3.13	47	4.25	63
b)	3.94	87	6.61	111	2.67	40	4.43	67
6.	4.87	109	8.52	133	3.65	43	5.20	61
7.	3.25	68	7.46	119	4.21	56	4.75	64
8. a)	4.00	89	6.06	93	2.06	34	2.89	48
b)	3.99	89	5.91	91	1.92	32	2.78	47
9. a)	2.18	70	4.26	103	2.08	49	2.34	55
b)	1.89	61	3.70	90	1.81	49	2.03	55
10. a)	3.57	86	5.54	92	1.97	36	2.57	46
b)	1.60	39	5.22	87	3.62	69	4.26	82
11.	4.24	76	7.34	106	3.10	42	5.01	68
12.	2.18	124	2.67	125	0.49	18	1.17	44
13.	3.59	90	6.76	129	3.17	47	3.85	57
Mean	3.28	85	5.66	107	2.38	41	3.23	57
S.D.	0.81	17.57						

TABLE II LUNG VOLUMES

b) EMPHYSEMA

SUBJECT	VC L	VC % Predicted	TLC L	TLC % Predicted	RV L	RV % TLC	FRC L	FRC % TLC
1. a)	3.13	82	6.01	109	2.88	48	3.82	64
b)	4.02	105	5.84	106	1.82	31	3.28	56
2.	4.57	102	7.25	142	4.68	51	6.21	67
3.	1.88	54	3.86	76	1.98	51	2.74	71
4. a)	4.04	97	6.75	112	2.71	40	3.96	59
b)	4.37	105	7.95	133	3.58	45	4.02	51
5.	1.95	53	4.47	84	2.52	56	3.35	75
6.	1.91	44	5.67	103	3.76	65	4.39	77
7.	3.46	68	6.85	93	3.39	49	4.86	71
8. a)	3.22	77	7.60	136	4.38	58	5.47	72
b)	3.41	81	6.94	124	3.53	51	5.03	72
9. a)	2.18	47	4.33	65	2.15	50	3.73	86
b)	2.81	61	6.16	93	3.35	54	4.44	72
10.	2.08	53	7.39	130	5.31	72	6.24	84
11.	1.85	56	4.55	103	2.70	59	3.25	71
Mean	2.99	72	6.11	107	3.25	52	4.32	70
S.D.	0.95	21.2						

TABLE III SPIROMETRY

a) ASTHMA

SUBJECT	FEV 0.5		FEV 1.0		MBC	
	L	% FVC	L	% FVC	L/min.	% Predicted
1.	1.03	38	1.54	57	37	47
2. a)	1.34	35	1.85	48	86	100
b)	1.06	30	1.52	43	63	73
3. a)	0.77	23	1.23	37	45	54
b)	0.67	19	1.03	30	32	39
4. a)	1.35	47	1.81	63	81	95
b)	0.93	32	1.39	48	82	95
5. a)	1.56	43	2.40	67	103	90
b)	2.34	59	3.30	84	160	140
6.	1.13	23	1.68	34	80	82
7.	0.71	22	1.10	34	43	38
8. a)	1.44	36	2.18	55	69	69
b)	1.26	32	1.88	47	37	37
9. a)	0.64	29	0.96	44	33	41
b)	0.35	19	0.58	31	22	27
10. a)	1.50	42	2.40	57	79	79
b)	0.22	14	0.32	20	14	14
11.	0.99	23	1.53	36	38	29
12.	1.46	67	1.99	91	67	93
13.	1.09	30	1.57	44	88	88
Mean	1.09	34	1.61	49	62.9	67
S.D.			0.54	17.39		18.69

TABLE III SPIROMETRY

b) EMPHYSEMA

SUBJECT	FEV 0.5		FEV 1.0		MBC	
	L	% FVC	L	% FVC	L/min.	% Predicted
1. a)	0.45	14	0.74	24	19	21
b)	0.74	18	1.09	27	39	43
2.	0.38	8	0.58	13	24	24
3.	0.26	14	0.38	20	11	13
4. a)	0.67	17	0.99	25	42	43
b)	1.15	26	1.65	38	77	84
5.	0.58	30	0.80	41	18	22
6.	0.19	10	0.32	17	12	11
7.	0.61	18	0.93	32	35	32
8. a)	0.51	16	0.76	24	31	34
b)	0.41	12	0.61	18	18	20
9. a)	0.38	17	0.58	27	20	18
b)	0.41	15	0.64	23	23	22
10.	0.22	11	0.32	15	12	13
11.	0.55	30	0.78	42	14	18
Mean	0.50	17	0.74	26	26.3	28
S.D.				8.86		17.8

TABLE IV LUNG COMPLIANCE AND AIRWAY RESISTANCE

a) ASTHMA

SUBJECT	CL	CL / FRC	Ri	Re	$\bar{R}$
	L/Cm. H_2O		Cm.H_2O/L/sec.	Cm.H_2O/L/sec.	Cm.H_2O/L/sec.
1.	.038	.017	7.61	12.51	10.06
2. a)	.109	.048	5.46	12.38	8.92
b)	.175	.07	1.53	4.37	2.95
3. a)	.102	.028	7.36	16.94	12.15
b)	.159	.045	6.63	11.19	8.91
4. a)	.059	.025	7.57	11.99	9.78
b)	.072	.028	10.14	8.66	9.40
5. a)	.106	.025	5.16	9.53	7.35
b)	.095	.021	8.33	10.13	9.23
6.	.140	.027	2.38	4.18	3.28
7.	.143	.030	5.23	10.53	7.88
8. a)	.105	.036	3.71	3.60	3.66
b)	.125	.045	4.20	4.38	4.29
9. a)	.048	.021	9.70	7.85	8.78
b)	.037	.018	9.56	12.99	11.28
10. a)	.062	.024	3.39	3.61	3.50
b)	.062	.015	7.37	11.56	9.47
11.	.168	.034	3.35	3.45	3.40
12.	.069	.059	5.61	6.82	6.22
13.	.101	.026	5.14	5.77	5.46
Mean	.099	.032	5.97	8.23	7.30
S.D.		.014		3.74	2.87

TABLE IV LUNG COMPLIANCE AND AIRWAY RESISTANCE

b) EMPHYSEMA

SUBJECT	CL L/Cm. H_2O	CL / FRC	Ri Cm.H_2O/L/sec.	Re Cm.H_2O/L/sec.	$\bar{R}$ Cm.H_2O/L/sec.
1. a)	.045	.012	4.22	12.68	8.45
b)	.098	.030	3.80	10.78	7.29
2.	.120	.019	3.87	17.53	10.70
3.	.054	.020	12.71	46.52	29.62
4. a)	.066	.017	8.72	35.16	21.94
b)	.074	.018	4.50	9.96	7.23
5.	.144	.043	7.01	8.53	7.77
6.	.077	.018	11.31	18.80	15.06
7.	.080	.016	4.34	10.65	7.50
8. a)	.051	.009	3.82	6.97	5.40
b)	.127	.025	4.89	10.63	7.76
9. a)	.082	.022	5.64	18.53	12.09
b)	.127	.029	3.06	6.99	5.03
10.	.071	.011	8.87	24.55	16.71
11.	.139	.043	4.39	5.95	5.17
Mean	.090	.022	6.08	16.28	11.18
S.D.		.0103		11.07	6.76

TABLE V ELASTIC AND RESISTIVE WORK*

a) ASTHMA

SUBJECT	INSPIRATORY RESISTIVE WORK	EXPIRATORY RESISTIVE WORK	ELASTIC WORK	ELASTIC AND EXPIRATORY RESISTIVE WORK
1.	3.51	1.67	3.70	5.37
2. a)	6.13	6.23	3.18	9.41
b)	1.89	3.51	2.12	5.63
3. a)	3.77	4.37	1.64	6.01
b)	2.26	2.52	1.06	3.58
4. a)	1.48	0.83	1.50	2.33
b b)	1.73	1.40	3.04	4.44
5. a)	7.14	4.12	6.07	10.19
b)	2.30	4.78	1.79	6.57
6.	1.25	1.06	1.01	2.07
7.	11.39	3.49	5.05	8.54
8. a)	4.08	1.76	2.47	5.23
b)	3.73	2.01	1.96	3.97
9. a)	2.95	1.54	1.45	2.99
b)	3.32	2.20	1.20	3.40
10. a)	2.65	1.33	2.62	3.95
b)	4.21	4.31	2.28	6.59
11.	0.92	1.16	0.81	1.97
12.	6.08	5.35	8.88	12.90
13.	3.49	3.36	1.30	4.66
Mean	3.71	2.85	2.66	5.49
S.D.		1.56	1.94	2.82

* All measurements in Kg. Cm.

TABLE V ELASTIC AND RESISTIVE WORK *

b) EMPHYSEMA

SUBJECT	INSPIRATORY RESISTIVE WORK	EXPIRATORY RESISTIVE WORK	ELASTIC WORK	ELASTIC AND EXPIRATORY RESISTIVE WORK
1. a)	2.19	1.76	3.27	8.79
b)	1.51	2.00	1.73	3.73
2.	2.00	3.26	1.21	4.47
3.	0.73	1.59	0.94	2.53
4. a)	1.14	2.83	2.40	5.23
b)	2.17	1.83	1.51	3.34
5.	2.20	1.43	1.17	2.60
6.	1.41	1.99	0.77	1.76
7.	4.62	2.28	2.00	4.28
8. a)	1.08	1.05	0.53	1.58
b)	4.12	4.99	1.60	6.59
9. a)	1.88	2.50	0.93	3.43
b)	1.69	1.70	0.64	2.34
10.	5.42	3.08	3.00	6.08
11.	1.63	1.42	2.03	3.45
Mean	2.25	2.25	1.58	4.01
S.D.		0.95	0.69	

* All measurements in Kg. Cm.

TABLE VI TOTAL ELASTIC AND RESISTIVE WORK*

a) ASTHMA

SUBJECT	TOTAL RESISTIVE WORK	ELASTIC & RESISTIVE WORK	TOTAL WORK
1.	5.18	8.88	7.34
2. a)	12.36	15.54	15.07
b)	5.40	7.52	7.25
3. a)	8.14	9.78	9.67
b)	4.78	5.84	5.76
4. a)	2.31	3.81	3.53
b)	3.13	6.17	5.87
5. a)	11.26	17.33	16.52
b)	7.08	8.87	8.66
6.	2.31	3.32	3.08
7.	14.88	19.94	19.29
8. a)	5.84	8.31	7.68
b)	5.74	7.70	7.18
9. a)	4.49	5.94	5.75
b)	5.52	6.72	6.61
10. a)	3.98	6.60	5.56
b)	8.52	11.80	10.65
11.	2.08	2.89	2.84
12.	11.43	20.31	18.42
13.	6.85	8.15	8.15
Mean	6.56	9.27	8.74
S.D.	3.48		4.76

* All measurements in Kg. Cm.

TABLE VI TOTAL ELASTIC AND RESISTIVE WORK*

b) EMPHYSEMA

SUBJECT	TOTAL RESISTIVE WORK	ELASTIC & RESISTIVE WORK	TOTAL WORK
1. a)	3.95	7.22	6.60
b)	3.51	5.24	4.81
2.	5.26	6.47	6.37
3.	2.32	3.26	3.11
4. a)	3.97	6.37	6.02
b)	4.00	5.51	5.47
5.	3.63	4.80	4.68
6.	3.40	4.17	4.04
7.	6.90	8.90	8.37
8. a)	2.13	2.66	2.65
b)	9.11	10.71	10.69
9. a)	4.38	5.31	5.23
b)	3.39	4.03	3.95
10.	8.50	11.50	10.21
11.	3.05	5.08	4.86
Mean	4.50	6.09	5.80
S.D.	2.02		2.28

* All measurements in Kg. Cm.

TABLE VII TIDAL VOLUMES AND MAXIMAL PRESSURES

a) ASTHMA

SUBJECT	V_T (Litres)	MAXIMAL NEGATIVE PRESSURE (Cm H_2O)	MAXIMAL POSITIVE PRESSURE (Cm H_2O)
1.	.556	17.7	7.14
2. a)	.843	15.1	12.4
b)	.843	6.8	7.4
3. a)	.627	11.2	13.4
b)	.627	9.0	7.2
4. a)	.400	9.2	3.3
b)	.522	13.2	4.2
5. a)	1.068	15.4	6.1
b)	.619	13.9	6.0
6.	.564	6.4	3.1
7.	.118	18.4	4.1
8. a)	.683	11.6	5.1
b)	.688	11.6	5.1
9. a)	.375	14.0	6.8
b)	.360	14.9	7.8
10. a)	.550	12.2	5.2
b)	.600	16.1	11.0
11.	.406	5.8	4.0
12.	.365	5.3	5.3
13.	.575	11.1	7.7
Mean	.569	11.95	6.62

TABLE VII TIDAL VOLUMES AND MAXIMAL PRESSURES

b) EMPHYSEMA

SUBJECT	V_T (Litres)	MAXIMAL NEGATIVE PRESSURE (Cm H_2O)	MAXIMAL POSITIVE PRESSURE (Cm H_2O)
1. a)	.334	8.7	4.6
b)	.334	8.8	7.2
2.	.539	7.2	8.6
3.	.328	7.1	8.5
4. a)	.404	14.1	14.1
b)	.440	11.4	7.7
5.	.576	7.5	3.5
6.	.338	11.3	6.1
7.	.575	16.4	9.9
8. a)	.233	8.8	6.0
b)	.678	10.3	9.7
9. a)	.390	11.0	8.2
b)	.400	8.1	8.7
10.	.935	13.7	5.1
11.	.675	7.5	3.7
Mean	.479	* 10.1	+ 7.4

* Mean values for male patients with asthma and emphysema, 13.93 and 10.24 respectively: Difference highly significant ($P < .01$).

+ Mean values for male patients with asthma and emphysema, 6.96 and 7.71 respectively: Difference not significant ($p > .7$).

TABLE VIII COMPARISON OF PAIRED VALUES

'x'	'y'	ASTHMA#	EMPHYSEMA#
VC (L;%)	CL/FRC	$r = 0.67$ $.01 > p > .001$	N.S.
VC (L;%)	Elastic work (Kg.Cm.)	N.S.	N.S.
VC (L;%)	Total resistive work (Kg.Cm.)	N.S.	N.S.
FEV 1.0 (% FVC)	Re (CmH_2O/L/sec.)	N.S.	$r = -0.98$ $.01 > p > .001$
FEV 1.0 (L)	CL/FRC	$r = 0.68$ $.02 > p > .01$	N.S.
FEV 1.0 (% FVC)	Exp. resistive work (Kg. Cm.)	N.S.	$r = -0.68$ $.05 > p > .02$
FEV 1.0 (% FVC;L)	Elastic Work (Kg.Cm.)	N.S.	N.S.
FEV 1.0 (%FVC;L)	Exp. resistive & elastic work (Kg.Cm.)	$r = -0.67$ $.01 > p > .001$	N.S.
MBC (% predicted)	Mean R. (CmH_2O/L/sec.)	N.S. (+)	N.S. (-) *
MBC (% predicted)	Total Work (Kg.Cm.)	N.S.	N.S.
MBC (% predicted)	Total Resistive Work (Kg. Cm.)	N.S.	N.S.

N.S. = not significant (upper limit of significance $p = .05$)

* Comparison of MBC/ $\overline{R}$ between asthma and emphysema highly significant (p .001).

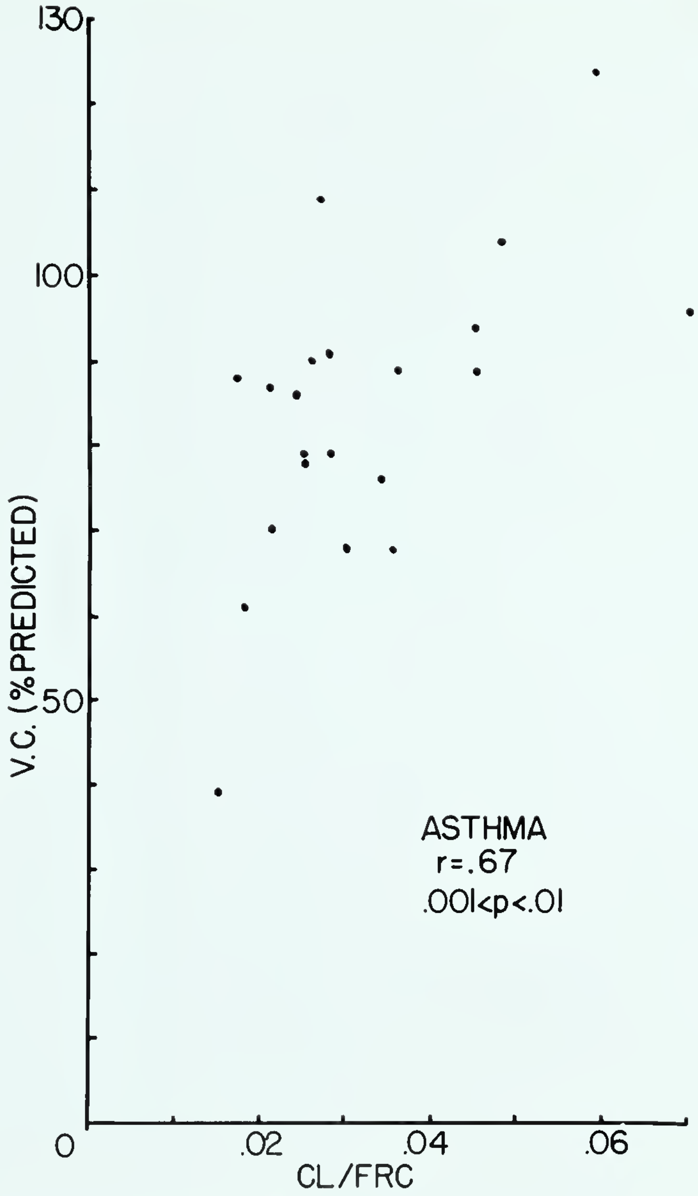

Figure V - A

Vital Capacity vs. Specific Compliance: Asthma

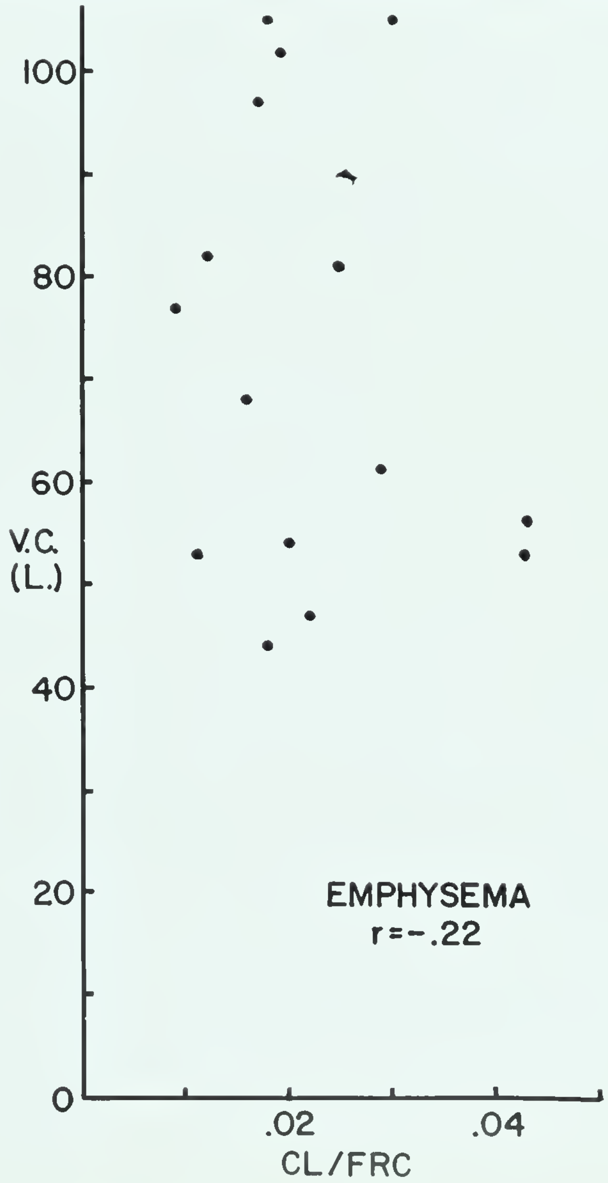

Figure V-B

Vital Capacity vs. Specific Compliance: Emphysema

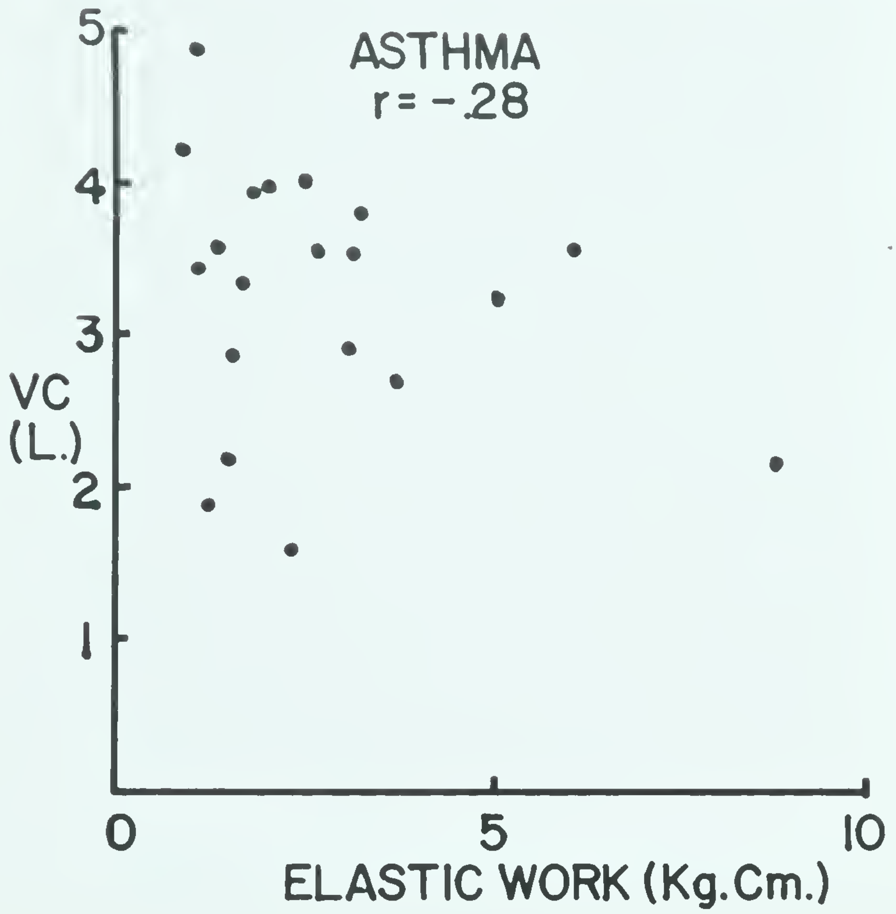

Figure VI - A

Vital Capacity vs. Elastic Work: Asthma

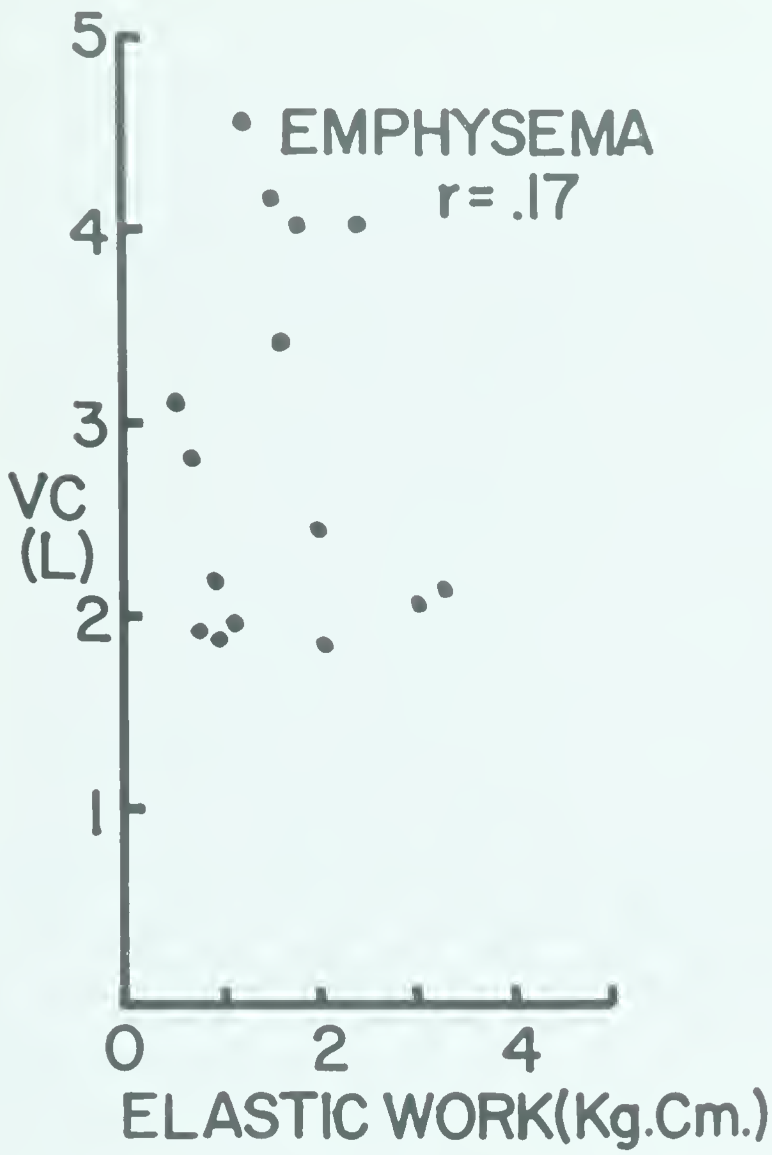

Figure VI - B

Vital Capacity vs. Elastic Work: Emphysema

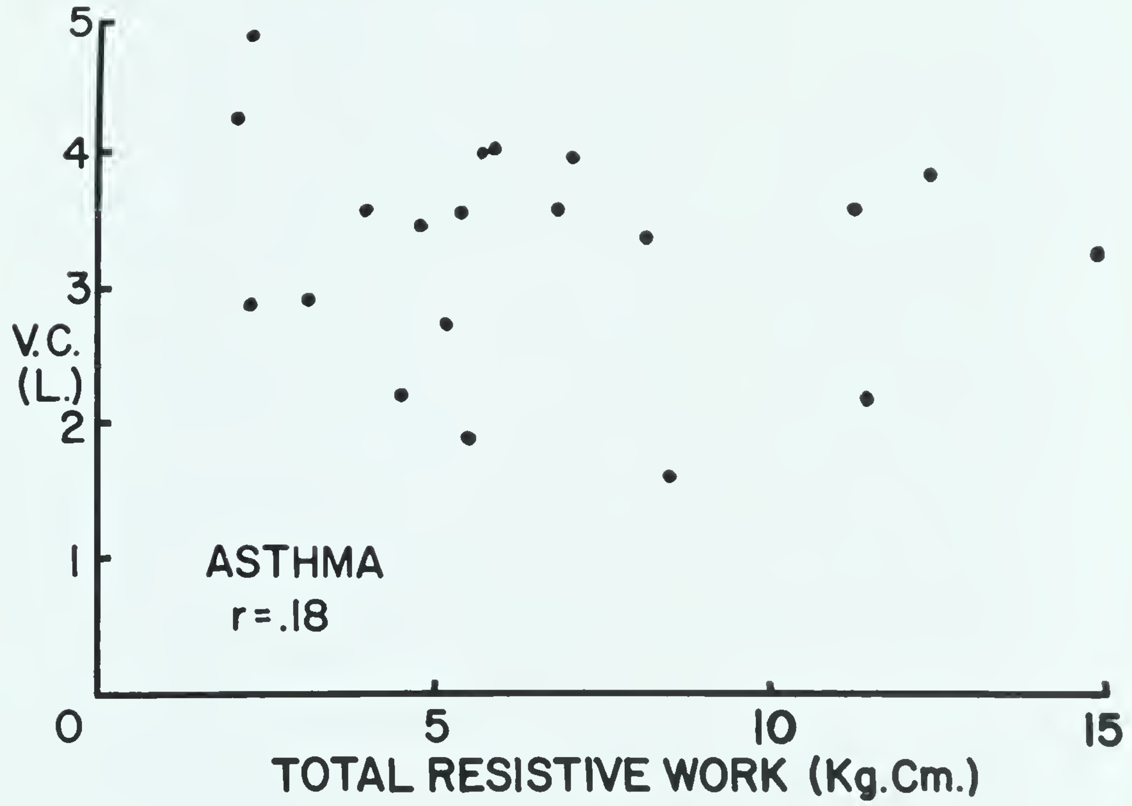

Figure VII - A

Vital Capacity vs. Total Resistive Work: Asthma

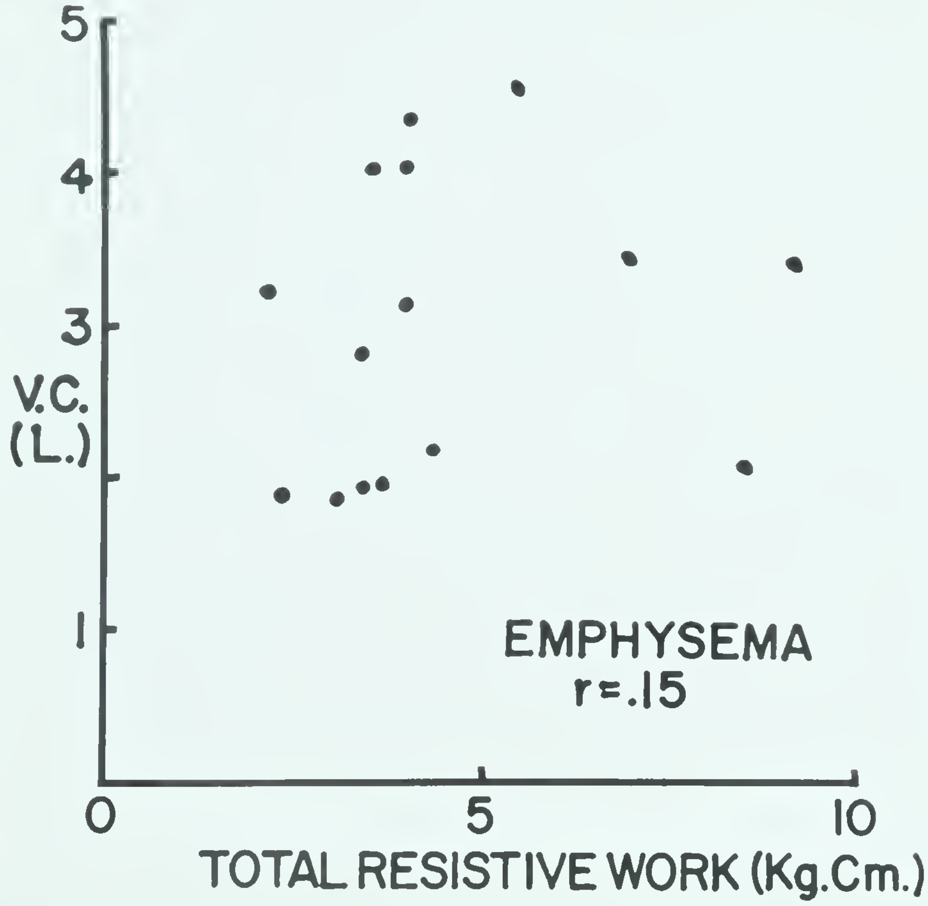

Figure VII - B

Vital Capacity vs. Total Resistive Work: Emphysema

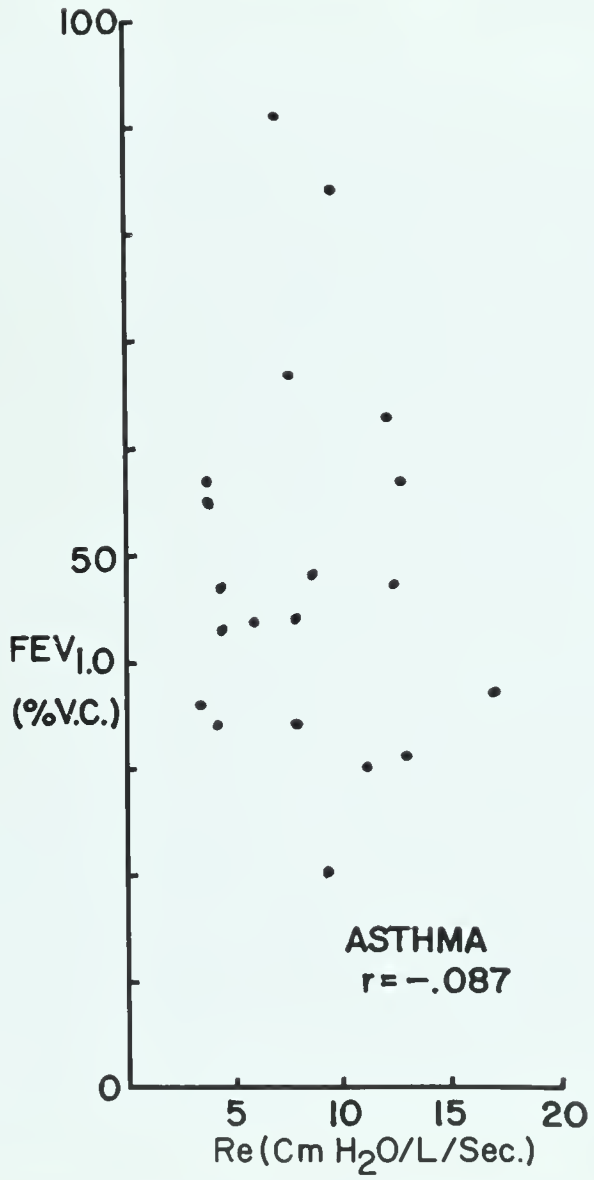

Figure VIII - A

Forced Expiratory Volume vs. Expiratory Airway Resistance:Asthma

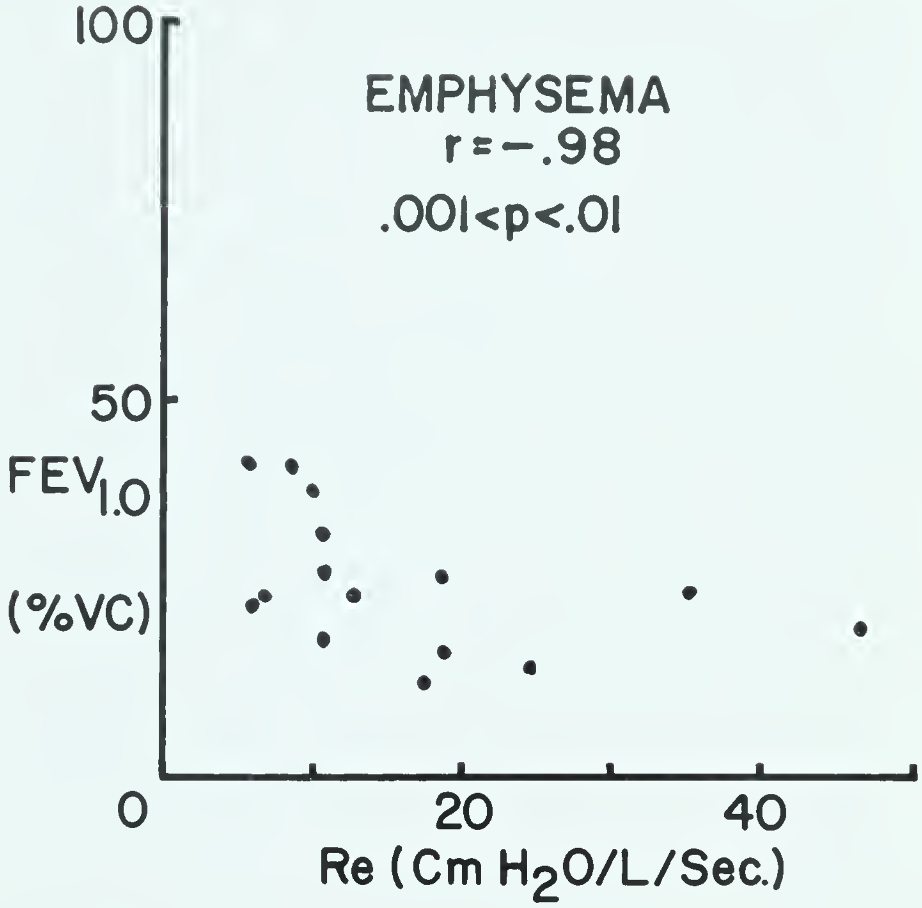

Figure VIII - B

Forced Expiratory Volume vs. Expiratory Airway Resistance: Emphysema

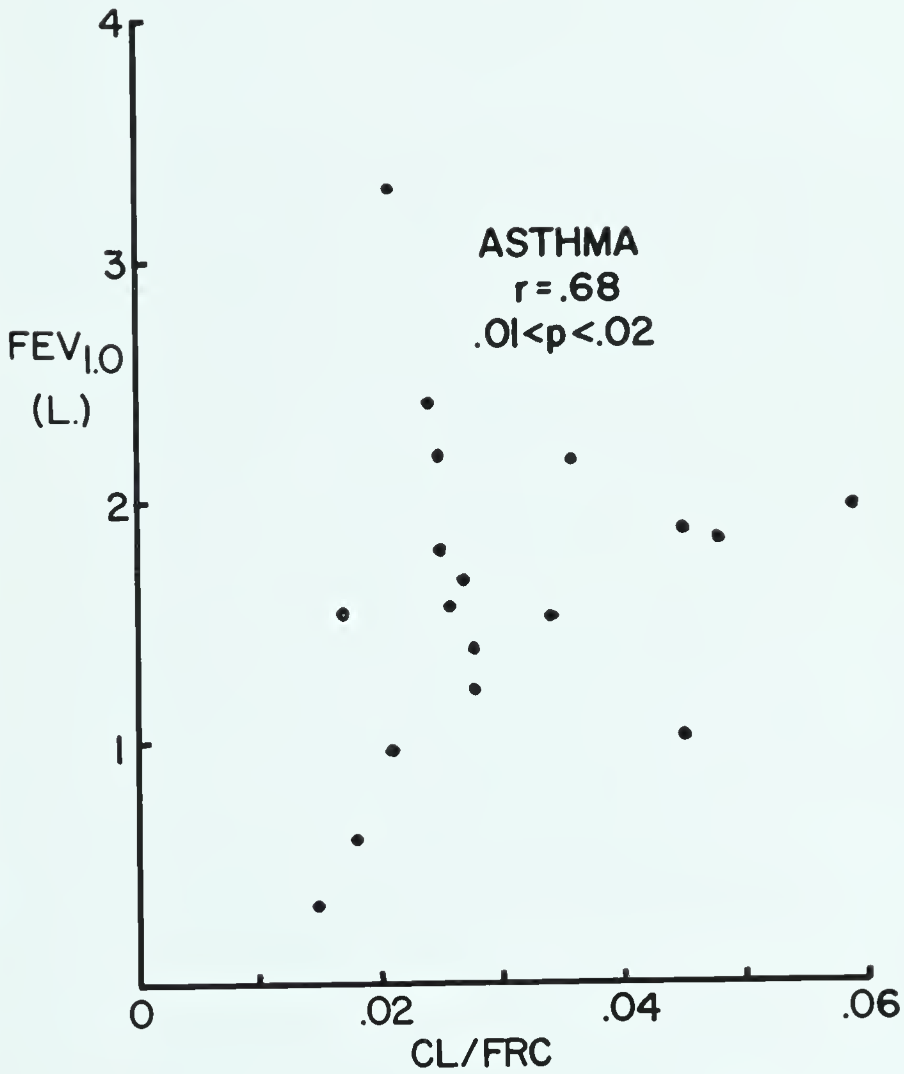

Figure IX

Forced Expiratory Volume vs. Specific Compliance: Asthma

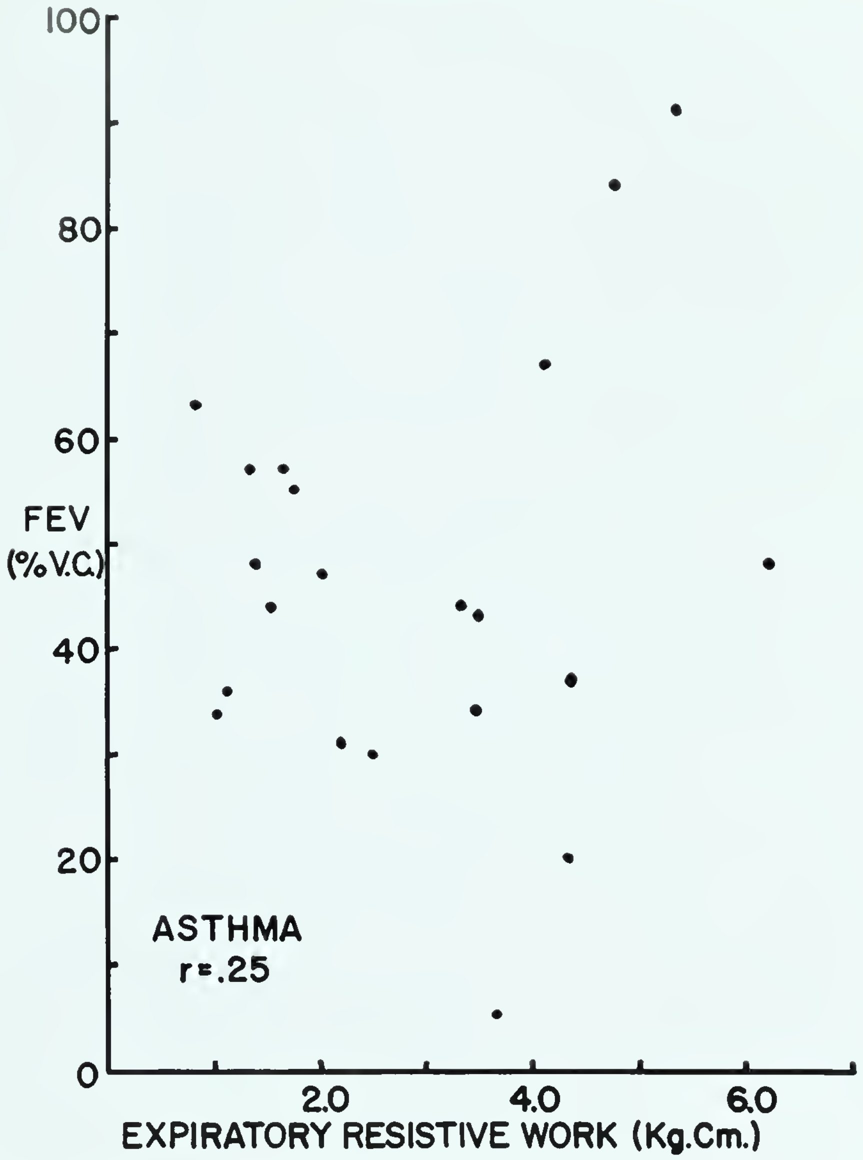

Figure X - A

Forced Expiratory Volume vs. Expiratory Resistive Work: Asthma

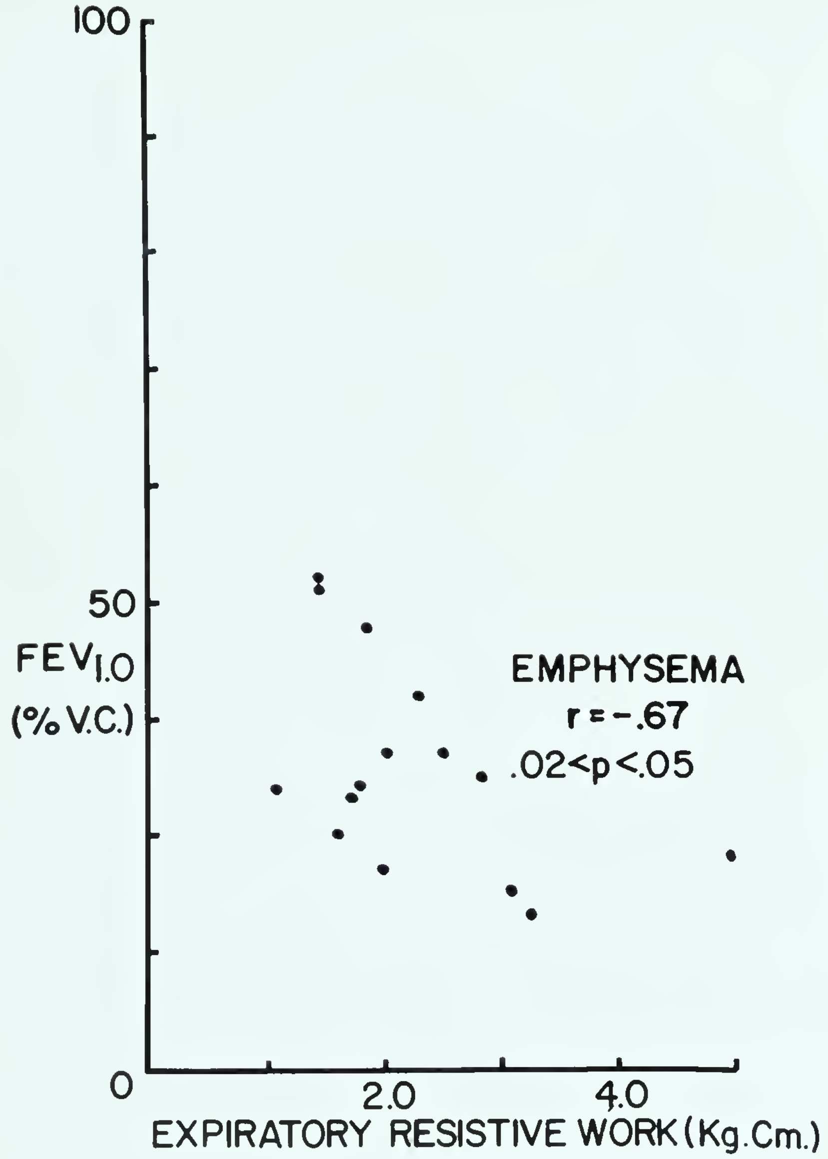

Figure X-B

Forced Expiratory Volume vs. Expiratory Resistive Work:Emphysema

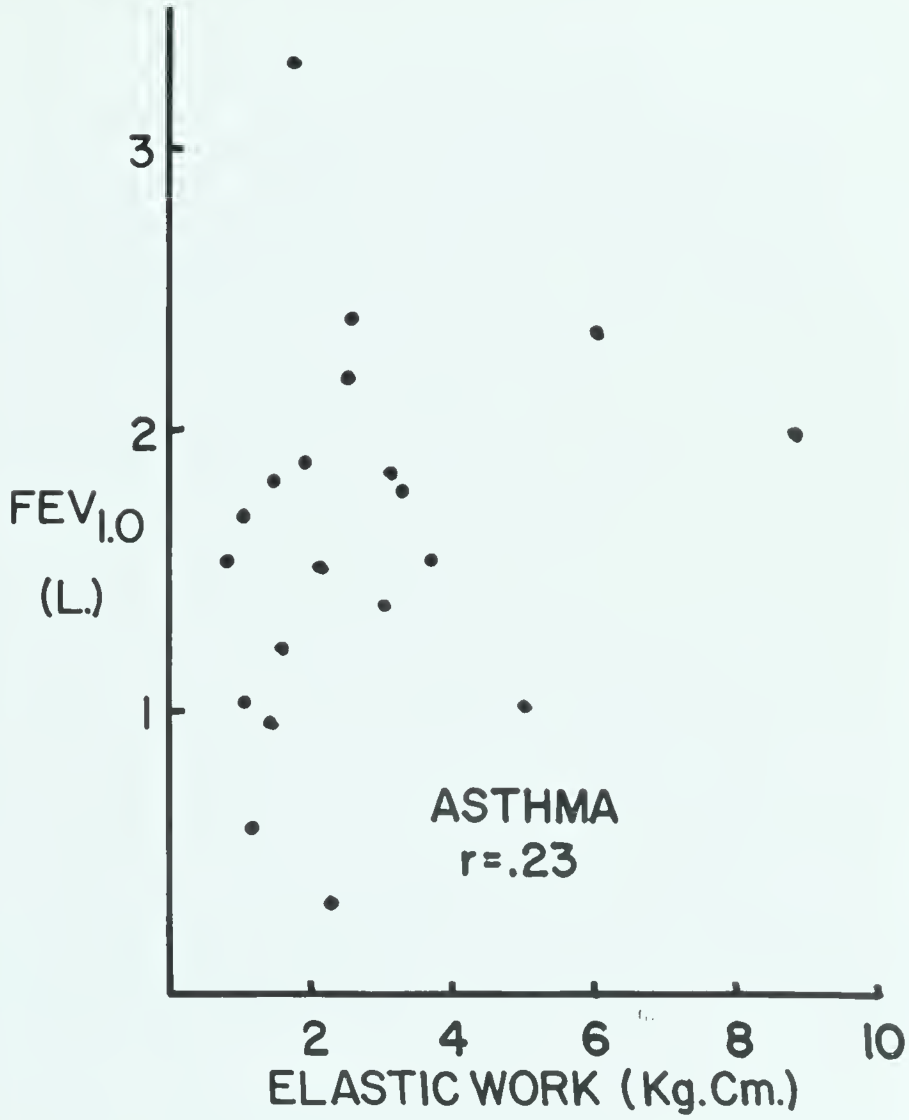

Figure XI - A

Forced Expiratory Volume vs. Elastic Work: Asthma

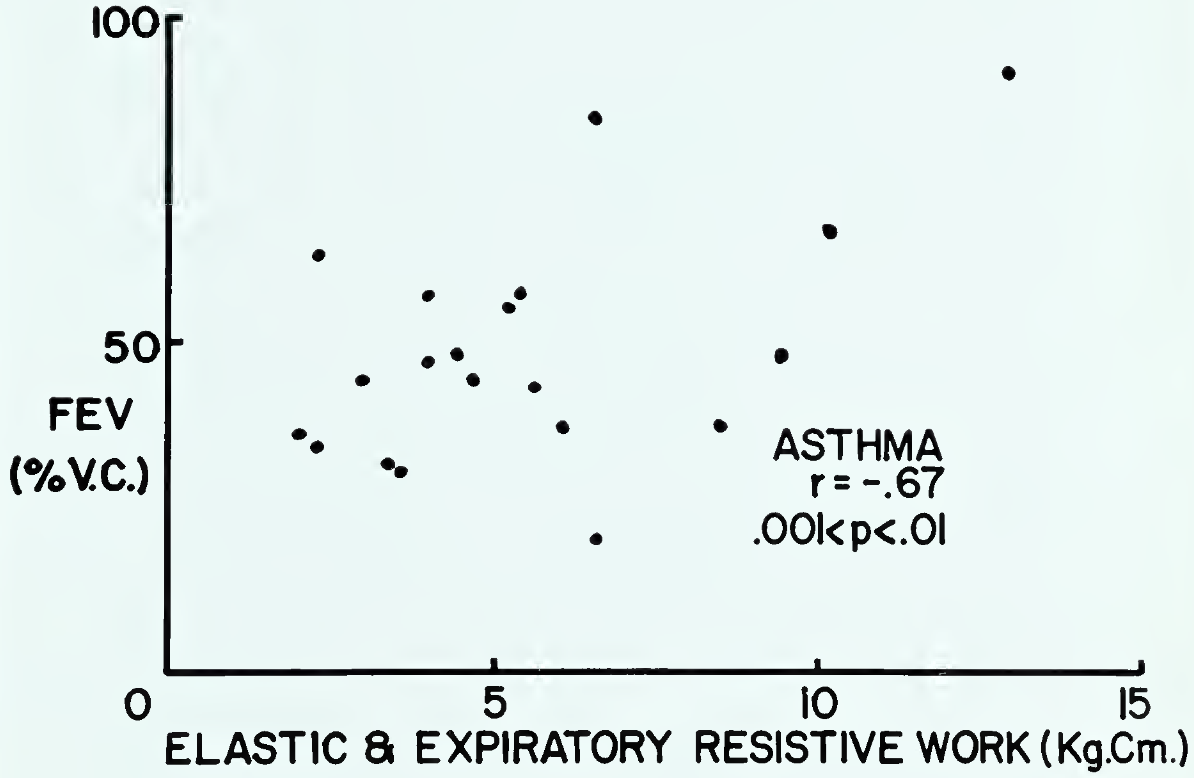

Figure XI - B

Forced Expiratory Volume vs. Elastic Plus Expiratory Resistive Work: Asthma

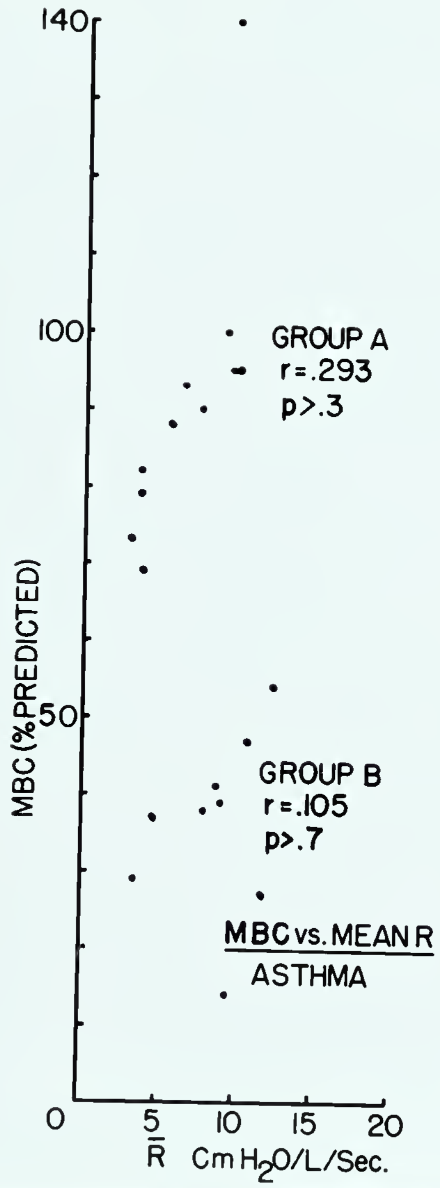

Figure XII - A

Maximum Breathing Capacity vs. Mean Airway Resistance:

Asthma

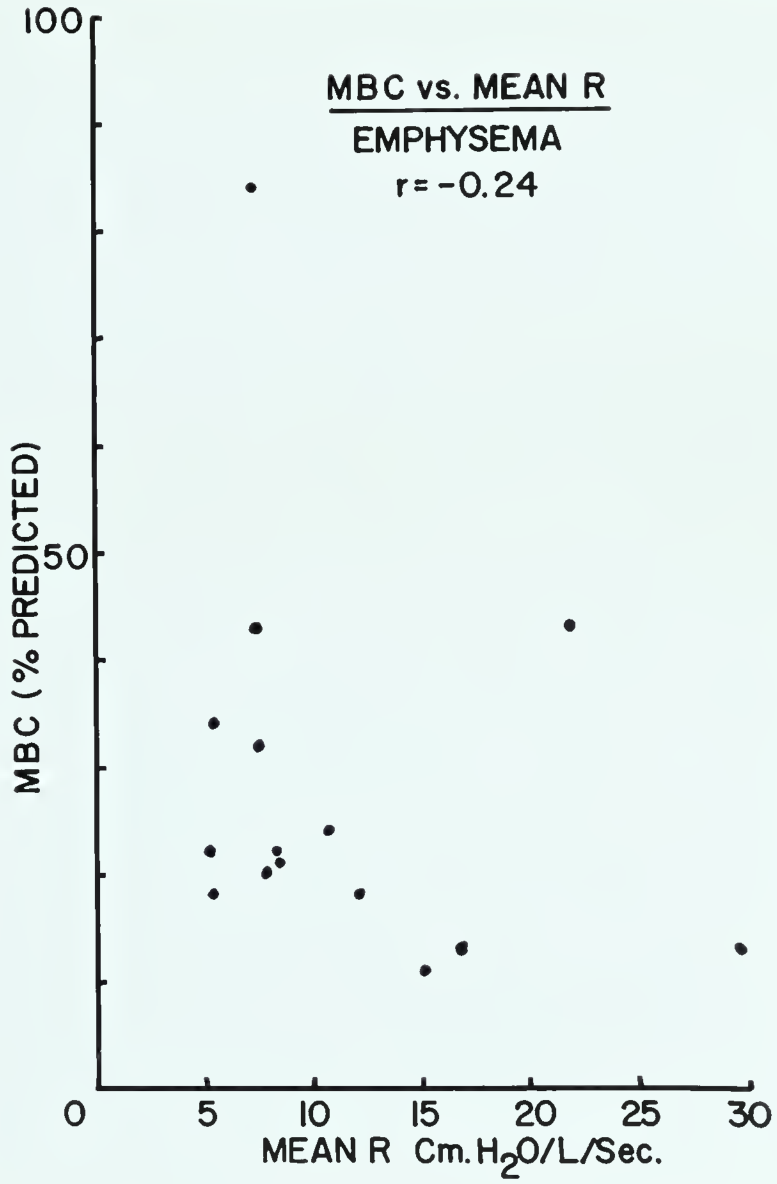

Figure XII - B

Maximum Breathing Capacity vs. Mean Airway Resistance:

Emphysema

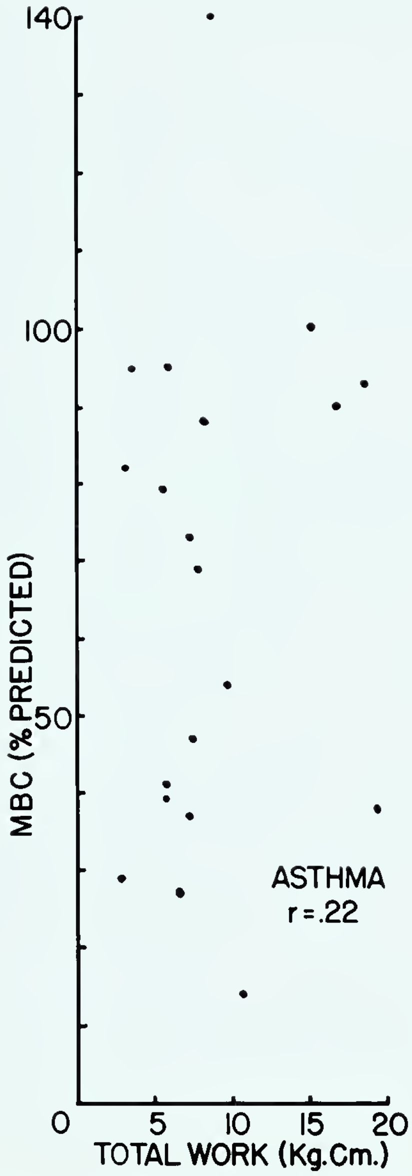

Figure XIII - A

Maximum Breathing Capacity vs. Total Work: Asthma

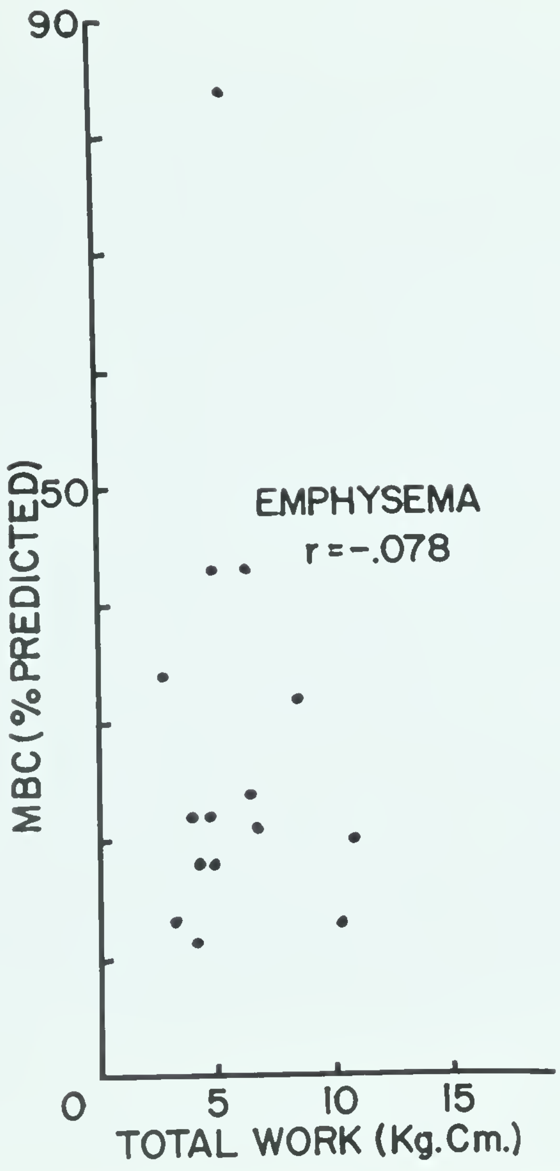

Figure XIII - B

Maximum Breathing Capacity vs. Total Work: Emphysema

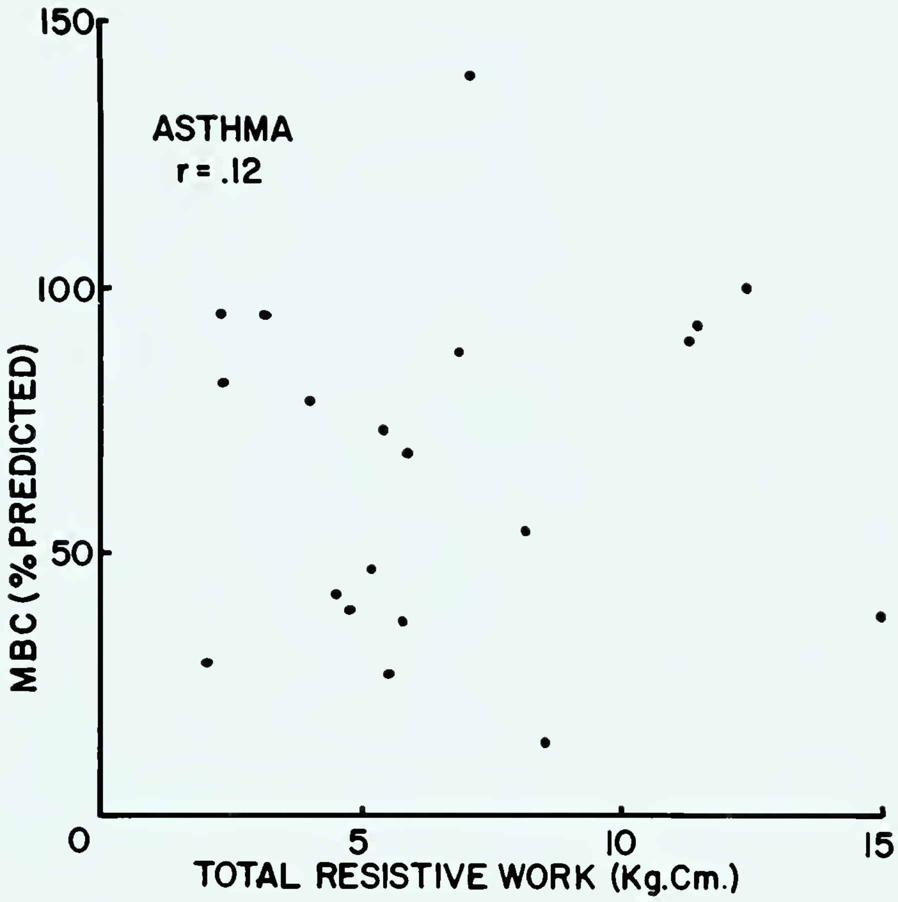

Figure XIV - A

Maximum Breathing Capacity vs. Total Resistive Work:

Asthma

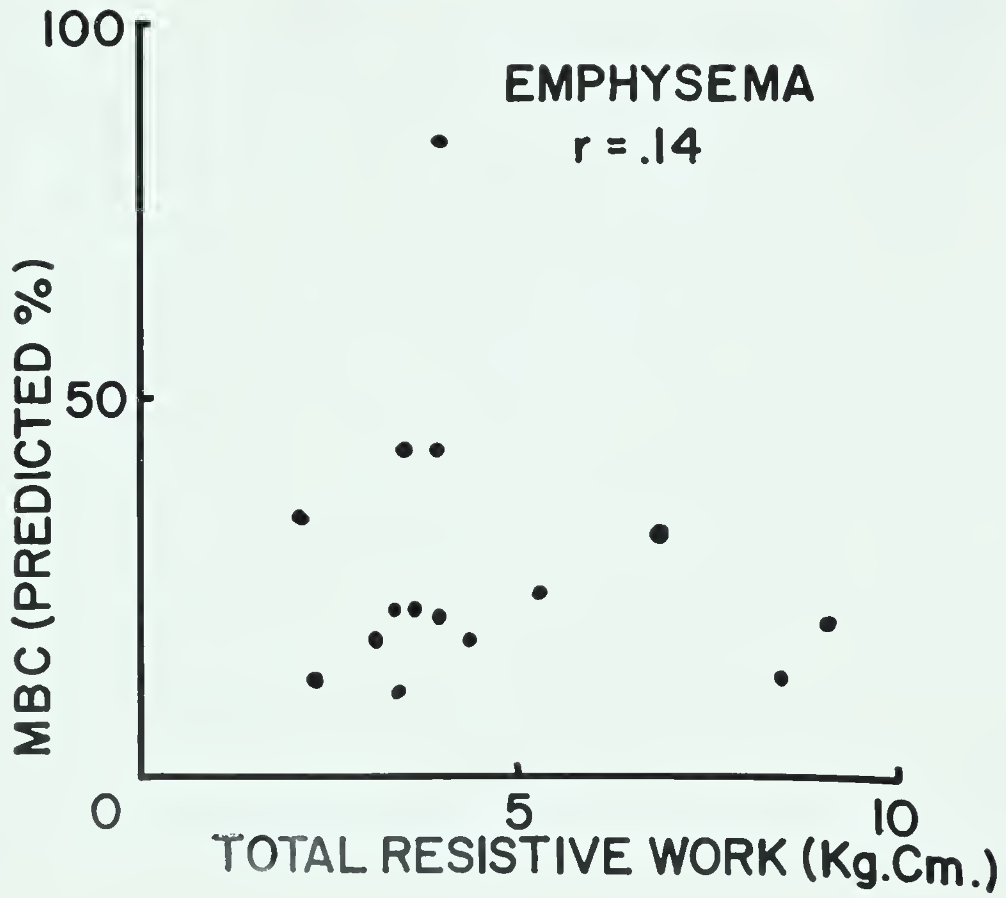

Figure XIV - B

Maximum Breathing Capacity vs. Total Resistive Work: Emphysema

RESULTS

Studies were carried out on thirteen asthmatic and eleven emphysematous patients. Some patients were investigated on two occasions, so that at the conclusion of the study a total of 35 sets of values for lung volume, spirometry and pulmonary mechanics were available for analysis. These raw data are presented in full in tables I - VII.

Age, Height and Weight. (Table I).

The mean values for the asthmatic group were 44.5 years, 64.7 in. and 151.4 pounds. For the emphysematous subjects the respective values were 60.4 years, 66.8 inches and 130.8 pounds. All but one of the latter group were male, and when these are compared with the eight male asthmatic patients, it is seen that while the emphysematous patients are somewhat taller than the asthmatic individuals (average height 69.2", compared with 67.8") they are also considerably lighter (133.3 pounds, compared with 166.9 pounds) as well as being significantly older (average age emphysematous patients 61.7 years, asthmatic subjects 50.3 years).

Lung Volumes and Spirometry

Lung volumes for the two groups are presented in tables II a and b, and values for the forced expiratory volumes and maximum breathing capacity in tables III a and b.

Total Lung Capacity

The average value for both groups was 107% predicted volume.

This is within normal limits (normal range 100± 15%).

Vital Capacity

For the asthmatic subjects this averaged 3.28 L (85% predicted normal). In the University of Alberta Hospital Laboratories 85% is arbitrarily regarded as the lower limit of normal, and the average figure for asthmatics therefore represents a value of borderline significance. Ten of the 20 observations were within normal limits (> 85% predicted values) and the remainder represented minor to moderate degrees of restriction (60-85%), with the exception of one reading on one subject during an episode of severe bronchospasm, when a VC of 39% predicted normal value was recorded.

The average value for the vital capacity in the emphysematous group was 2.99 L (72% predicted value). There was a considerable variation between individual subjects. Values ranging between 1.91 - 4.56 L (44 - 105%). Four of the 15 observations could be considered normal, five represented moderate restriction, and six were more severely restricted (VC 40 - 60% of normal).

While the emphysema patients tended to show somewhat more restriction than did the asthmatic group, the difference was not significant ($p > .05$).

Tidal Volume (Table VII)

This averaged .569 L for the asthmatic subjects, and 4.79 L for the emphysematous patients. It is of some interest that these values

were equivalent to 17% VC for the former group, and 16% VC for the latter, indicating that both groups were operating at a higher than normal level.

Functional Residual Capacity (Table II)

The upper limit of normal for this value is taken to be 45% TLC in this laboratory. While both groups had an elevated FRC, the level was higher in the emphysematous subjects (average value 70%) than in the asthmatic patients (average value 57%).

Residual Volume (Table II)

It has often been claimed that the ratio RV/TLC % is a useful diagnostic index of emphysema.[52,102] The upper limit for this value, even in older subjects, is taken to be 40%.[19] Both groups of subjects in the present study were found to be abnormal in this respect, but the emphysematous patients were considerably more hyperinflated (average value 52%) than the asthmatics (average value 41%), and the difference between the two groups in this respect was highly significant ($p < .01$).

Forced Expiratory Volumes (Table III)

For the reasons outlined previously, calculations were based on the FEV 1.0. The normal value for this is taken as 85%, with a lower limit of 75%.

The average value for the asthmatic subjects was 49% VC, and for the emphysematous group 26% VC. The gross obstruction evidenced by

the latter is in keeping with current concepts concerning the pathophysiology of emphysema, in which it is believed the airways collapse partially or completely during expiration (the so-called "ball-valve" effect) with a resultant diminution in flow rate.[25,26,45,63]

Maximum Breathing Capacity (Table III)

This is expressed as a percentage of a predicted normal value, the range of which is 80 - 120%.

Both groups demonstrated a decrease in the MBC, the average figure for patients with asthma being 67% and for the emphysematous subjects 28%. It will be seen from Table III and Figure XII-A, however, that the asthmatic group was apparently composed of two distinct populations; those who retained near normal maximal ventilatory capacities (MBC 69%, average value 91%), and a second group whose capacity was seriously impaired (average MBC 36% predicted normal). Among the factors concerned in determining a given asthmatic's MBC (in addition to the patient's cooperation) are age, sex, height and muscular development, as well as the duration and severity of the disease process. In comparing the eleven individuals in Group A (near normal ventilatory capacity) with the nine subjects in Group B (severely reduced MBC) the only apparent difference that could be determined lay in the duration of the disease (average duration 24.5 years and 14.1 years respectively) but this was not statistically significant ($p > .05$).

STUDIES OF PULMONARY MECHANICS

Lung Compliance (Table IV)

There has been a wide variation in the normal values previously reported for lung compliance in the literature.[12] In a study carried out in this laboratory[79] the value for CL in ten otherwise normal male smokers, aged 21 to 35 years, was 0.135 L/Cm.H_2O which is in close agreement with the lower estimates in the literature.

In the present investigation, utilizing the same techniques as the previous study, the mean value for CL in asthmatic subjects was 0.099 L/Cm. H_2O, the average for the emphysematous patients 0.090 L/Cm.H_2O. In both groups there was a wide range between individual subjects (for asthmatics .037 - .175; for the emphysematous .045 - .144). This represents differences in sex and physique as well as the severity of the disease process. When the specific compliance (CL/FRC) is calculated, mean values for the two groups are .032 and .022 respectively, in contrast to normal adult values of .05 - .06.[19]

Inspiratory Airway Resistance (Table IV)

The average value for this was 5.97 for the asthmatic group, and 6.07 Cm.H_2O/L/sec. for the emphysematous subjects. These are in keeping with previously reported figures, and represent values of some two to three times normal (average value 2.2, range 1.2 - 3.4 Cm. H_2O/L/sec.[19]). While it is to be expected that Ri will be increased in

asthmatic patients, on theortetical grounds it is less easy to explain the increase in emphysematous subjects. One might expect that the over compliant small airways would tend to dilate during inspiration, with no increase in the resultant resistance. In the absence of the other data, it is concluded that the observed high values for Ri probably represent the effects of chronic bronchitis, which is frequently present as an important functional element of the emphysema syndrome;[15,37,91] although the possibility that the high inspiratory resistance results from uneven ventilation caused by permanent distortion of the lung architecture cannot be dismissed.

Expiratory Airway Resistance (Table IV)

The mean value for the asthmatic group was 8.23 Cm.H_2O/L/sec. and for the emphysematous group 16.28 Cm.H_2O/L/sec. This difference reflects the grossly reduced flow rate which is noted during expiration in emphysema.

Mean Airway Resistance (Table IV)

This is calculated by dividing the sum of inspiratory and expiratory resistances by two (Ri + Re/2). In the present study the average values were 7.30 and 11.18 Cm.H_2O/L/sec. for asthmatic and emphysematous subjects respectively. These values agree well with previously reported figures. Macklem and Becklake[62] reported an average airflow resistance of 7.4 Cm./L/sec. in patients with an FEV reduced to

57% predicted value. (In our series the asthmatic subjects averaged 56% predicted FEV 1.0). They reported airway resistances of five times normal in emphysematous subjects, assuming a normal value of approximately 2 Cm.H_2O/L/sec., which again is in close agreement with the results of the present study.

WORK OF BREATHING

Elastic Work (Table V)

This represents that portion of the work of breathing which is performed during inspiration, stored as potential energy, and released again to assist in the process of expiration. In the present series the average for elastic work was 2.66 Kg.Cm. in the asthmatic group, and 1.58 Kg. Cm. in the emphysematous group. Since elastic work is proportional to the square of the tidal volume, a part of this difference was attributable to the difference in the tidal volumes at which the subjects in the two groups operated. The value for the emphysematous patients agrees well with the figures of Miller, Gall, and Sproule[80] who reported a mean value of 1.74 Kg.Cm. in ten emphysematous subjects studied prior to the administration of bronchodilator.

Resistive Work (Tables V and VI)

This was subdivided into inspiratory and expiratory resistive work. The mean values for fractions were 3.71 and 2.85 Kg.Cm. in the

asthmatic group, and 2.25 and 2.25 Kg.Cm. in the emphysematous group. Thus the total resistive work for the two groups was 6.56 and 4.50 Kg.Cm. respectively. The latter figure again shows fair agreement with the values of Miller et al[80] who reported a mean resistive work value of 3.82 Kg.Cm. in patients who appear to have been rather less severely affected (as evidenced by a slightly higher FEV and slightly less hyperinflation).

It will be noted that the present values are lower for the patients with emphysema, in spite of the fact that airway resistance was higher in these subjects. The explanation of this apparent paradox lies in the fact that while work within the context of the pulmonary system is equal to the product of pressure and volume, resistance is the ratio of pressure to flow. In asthma high pressures are necessary to bring about adequate gas exchange, but the resultant respiratory volumes are near normal. In emphysema, on the other hand, the maximal intrapleural pressure which can be generated is reduced as a result of loss of elastic recoil in the lung. Resistance remains high, however, because reduced volumes are expired over a grossly prolonged period of time; which results in very low flow rates per unit time. (It will be seen from Table VII that a highly significant difference existed between the maximum negative intrapleural pressure for male asthmatic and emphysematous patients respectively ($p < .01$).

It is less easy to explain why, though there is considerable individual variation, the average values for inspiratory resistive work should exceed those for expiratory resistive work. This has not generally been reported in the past, though in scrutinizing the results of previous investigators[80] it is noted that individual subjects, in other series showed the same tendency, so that with the larger number of patients studied in the present series it is possible that such a trend might assume increasing importance. However on theoretical grounds, taking into account the effect of warming the inspired air and variations in the R.Q. (that is, $\dot{V}\ CO_2\ /\ \dot{V}\ O_2$) which may serve to explain some individual variation, the expired volume is nevertheless approximately equal to or slightly greater than the inspired volume of air. Table VII shows that the difference in the work of inspiration and expiration probably results from the difference in the pressures exerted during the two phases of respiration. (This is not to say that the maximum negative intrapleural pressure which can be generated exceeds the maximum positive pressure; at least in normal subjects the data of Rahn et al[89] indicate the reverse to be true, although the numerical difference is not great for the level of lung inflation at which the subjects in the present study functioned). The present investigation was concerned with functional rather than maximal pressure gradients in patients with lung pathology, and the

observed fact that these were less during expiration indicates that the elastic work forms a significant fraction of the force with which expiration is effected. If the expiratory resistive and elastic work fractions are summed, the resultant always exceeds the inspiratory resistive work: the average figures for the former being 5.49 and 4.01 Kg. Cm. for the asthmatic and emphysematous groups respectively.

COMPARISON OF PAIRED VALUES

(Table VIII)

The following comparisons were made, employing the techniques of the "paired - t" test.[7] The significance of the value calculated was determined by reference to standard tables,[33] the upper limit for significance being taken as p = .05.

1. Vital Capacity and Specific Compliance:

The reasons for relating the compliance as measured to the FRC have been outlined previously. When this was compared with the vital capacity measured in litres, no correlation was found in the emphysematous subjects. This confirmed previous reports[25,30,49,59,74,88] that in conditions characterized by airway obstruction, where the time constant, RC, varies for different paths of flow within the lungs, no correlation exists between the vital capacity and lung compliance. However in the case of the asthmatic patients a significant correlation between these paired values

was demonstrated ($r = 0.67$, $.001 < p < .01$). While this is contrary to most previous reports, the probable explanation lies in the fact that in the majority of previous studies compliance has not been related to lung volume. It has already been indicated that such a precaution is essential when comparing persons of different lung volume.

2. Vital Capacity and Elastic Work

When the vital capacity (whether measured in litres or as a percentage of the predicted value) is compared with the elastic work of breathing expressed in Kg. Cm., no correlation is found for either asthmatic or emphysematous subjects. The failure to observe any correlation in the asthmatic patients (amongst whom VC was related to CL) may in part be explained by the fact that, while compliance is a function of the tidal volume, the elastic work of breathing is a function of the square of the tidal volume.

3. Vital Capacity and Total Resistive Work

Again no correlation could be found between the vital capacity, expressed in litres or as a percentage, and the sum of the inspiratory and expiratory resistive work.

4. FEV 1.0 sec. and Expiratory Resistance

When the FEV 1.0, expressed as a percentage of the subject's vital capacity is compared with the expiratory resistance measured in Cm. H_2O/L/sec.

no correlation exists for the asthmatic group of patients. In emphysema, however, a highly significant degree of negative correlation is found. For this group the coefficient of correlation ('r') is -0.98 ($0.01 > p > .001$). As a result, if the two groups are considered together, an r value of -0.57 is obtained ($.01 > p > .001$). The significance of this in the light of previous results will be discussed later in the thesis.

5. FEV 1.0 and Specific Compliance.

Since a close correlation was found between FEV 1.0 and Re in emphysema but not in asthma, the possibility occurred that in the latter condition the FEV 1.0 might correlate with lung compliance, inasmuch as volume-flow raltions in the lungs are determined by the time constant.[70] This relationship can be expressed by the equation $V/\dot{V} = -RC$

When the comparison was made, it was found that a statistically significant correlation existed ($r = 0.68$, $.02 > p > .01$).

6. FEV 1.0 and Expiratory Resistive Work

No correlation existed between these two values in the case of the asthmatic subjects. A significant negative correlation was found for the patients with emphysema, though it was less close than for FEV and Re. ($r = -0.68$, $.05 > p > .02$)

7. FEV 1.0 and Elastic Work

No correlation existed for either group.

8. FEV 1.0 and Expiratory Resistive and Elastic Work

No correlation existed in the case of patients with emphysema. For the asthmatic group of patients, there was a significant negative correlation ($r = -0.67$, $.01 > p > .001$). It is somewhat difficult to explain this fact in the absence of any correlation for either elastic or expiratory resistive work separately. Presumably in the measurement of the work loop an imprecise distinction is made between the elastic and expiratory resistive components. Previous investigators have commented on this fact[79] which would also help to explain the otherwise strange phenomenon of the expiratory resistive work being less than the inspiratory resistive work. It is also reasonable that, though the elastic and expiratory resistive fractions are individually insignificant, together they form a whole which is related in a meaningful fashion to the forced expiratory volume.

9. Maximum Breathing Capacity and Mean Resistance

It has already been indicated that the asthmatic subjects divided themselves into two groups, here referred to as Group A and Group B, on the basis of whether or not they retained a normal ventilatory capacity. These, together with the emphysematous subjects, provided three groups (numbering eleven, nine and fifteen persons respectively) for whom comparisons of MBC and mean resistance were made. In no case was a significant correlation formed ($p > .3$). It was noted, however, that whereas the trend tended

to be towards a negative correlation in the case of patients with emphysema, there tended to be a positive relationship between the two values for the asthmatic subjects. In order to determine whether this difference was statistically significant, a synthetic value representing MBC/ $\bar{R}$ was calculated for each individual, and an unpaired t - test carried out between the groups. The difference between the asthmatic and emphysematous subjects was found to be highly significant ($p < .001$).

10. Maximum Breathing Capacity and Total Work

No significant correlation existed for either group.

11. Maximum Breathing Capacity and Total Resistive Work

No correlation could be found between these measurements in either group.

DISCUSSION OF RESULTS

The present results suggest that in patients with emphysema, the only measurement made in a routine pulmonary function laboratory which can be correlated with the results of pulmonary mechanics studies is the forced expiratory volume 1.0 sec. This finding is of some interest inasmuch as the measurement is made during the performance of a markedly abnormal manoeuvre, quite unlike the normal respiratory pattern. In spite of this, an excellent negative correlation is obtained between the FEV 1.0 and the expiratory resistance in the case of emphysematous subjects. The value for the coefficient of correlation, r, of -0.98 indicates that in these patients FEV

and Re are closely and significantly related; a finding which is in agreement with the views generally held by clinicians regarding the relationship between these two parameters in all cases of airway obstruction. However, there is comparatively little direct evidence to support this generalization, and our present findings indicate that amongst the asthmatic subjects no such correlation in fact exists. It has already been noted that when the two groups are considered as a whole, a correlation is again found which, while of lower degree ($r = 0.57$), remains significant ($.001 < p < .01$). It is believed that these findings may explain the apparent contradiction which exists between the previous reports of Lloyd and Wright[61] and Stein et al.[100] The former investigators, by inducing bronchospasm with an aerosol of amorphous silica, in effect produced a temporary population of pure asthmatics. The fact that they were unable to determine any correlation between FEV 1.0 and Re agrees with the results of the present study. Stein et al, on the other hand, studied patients with chronic obstructive lung disease. The precise diagnoses for these individuals is not indicated, but inasmuch as patients of different sex and age were studied it seems reasonable to suppose that the subjects investigated included both asthmatic and emphysematous individuals. If any patients with emphysema were in fact included in the series, present results suggest that the ensuing population would not be a homogeneous one, and the finding of a statistically significant correlation ($p = 0.1$)

therefore becomes of doubtful clinical importance. The same argument can certainly be applied to the work of Lefcoe[57] who compared the FEV 1.0 with the reciprocal of resistance, conductance, in a variety of normal, cardiac and pulmonary patients. The coefficient of correlation between these two parameters in his series was 0.57, the same value which obtains if both groups in the present study are considered as a whole.

The finding that in asthmatic subjects lung compliance and expiratory airway resistance are meaningfully related is of considerable interest, since so far as is known, this has not previously been reported. It must of course be realized that the existance of a statistically significant correlation does not necessarily imply a causal relationship. However, microscopic studies provide some support for the suggestion that it may be lung compliance which is the critical factor in determining the over all pulmonary function of asthmatic individuals. Autopsies performed on patients dying in status asthmaticus demonstrate extremely tenacious plugs of inspissated sputum in virtually all cases,[77] areas of atelectasis in nearly 50% of cases and bronchiectasis with associated fibrosis in about a quarter of the patients.[28] All these findings would lead to reduced lung compliance. In contrast evidence of bronchial muscle spasm and constriction is at best equivocal[11:132] (though it is debatable to what extent such changes might be expected to be detectable post mortem). Patients with bronchial asthma dying from other causes,

on the other hand, show only slight thickening of the basement membrane of the bronchioles;[103] a state which would doubtless give rise to increased airway resistance without materially affecting the lung compliance. While only limited conclusions can legitimately be drawn from pathological studies such as these, it seems reasonable to infer that the changes noted in patients dying in status asthmaticus vary only in degree from those which can be expected in subjects with severe though non-fatal asthma (amongst whom most of our patients can be classified).

It was further found that in emphysema the FEV 1.0 was related to expiratory resistive work, though the correlation was neither as close nor as significant as for FEV 1.0 and Re. Amongst the asthmatic subjects, on the other hand, the FEV 1.0 showed a correlation with the sum of the elastic and expiratory resistive work which was even more significant than the relationship between FEV 1.0 and CL. It seems possible that these observations may partially be explained by certain inaccuracies inherent in measuring the different fractions of the work loop; while in the case of the asthmatic individuals the results obtained may also reflect the complex interaction of elastic and resistive forces.

Although a confidant diagnosis of emphysema can be made only on histological evidence (which is rarely forthcoming during life)[34] it is believed that the present groups are assigned as carefully as possible according to all usually available diagnostic criteria. Many

of the individuals were studied intensively as a part of the evaluation of specific therapy for asthma and emphysema respectively. In the light of the history and results of physical examination and x-rays as well as a battery of pulmonary function and blood gas studies, it was felt that, within the limits of clinical confidance, all but two of the patients had been correctly assigned. In the case of subjects 9 and 10 in the asthmatic group it was believed that, while the original diagnosis had probably been bronchial asthma, at the time of the present investigation the presence of a significant degree of pulmonary emphysema could not be excluded.

The relative purity of pathology which, it is hoped, characterized the two groups is important because as a result of this investigation a clear pattern emerges of two diseases, clinically often difficult to distinguish, yet differing profoundly in their pathophysiology.

The average age of the emphysematous patients is somewhat older than in the majority of studies previously reported[11:186] which is understandable in view of the fact that these subjects generally represented a far advanced form of the disease. It is of interest to note that, while male subjects with emphysema were on average 1.4" taller, the mean weight of the male asthmatic patients was $33\frac{1}{2}$ pounds greater.

If these figures are regarded as an extimate, albeit a crude one, of the patients' general physique, it is inferred that the asthmatic patients were generally more muscular. There is also suggestive evidence for this in the fact that the average negative intrapleural pressure generated was significantly greater in the case of the asthmatic individuals. Two additional factors can be expected to contribute to the latter phenomenon. The negative intrapleural pressure generated by a patient with emphysema will be limited by the degree to which the lung tissue has lost its elasticity; and in the absence of normal elastic recoil, increasing positive pressure gradients must be developed during expiration (a phenomenon confirmed during the present investigation). Secondly, the inspiratory muscles of a patient with emphysema are working at a mechanical disadvantage as a result of the increasing thoracic deformity.

In line with this view of the two disease processes, despite a decrease in dynamic estimates of the lung compliance in emphysema, the actual compliance of the lungs (regarded as a function of the parenchymal tissue rather than a mere arithmetical ratio) imposes no limits on ventilation; and the factor which is critical to the patient's well being is his ability to generate adequate but not excessive pressure gradients. In all this the walls of the airways can be said to play a purely passive role, reacting in an entirely predictable fashion to any given pressure "stimulus". (In support of this contention, there is substantial evidence

from animal experimentation that even in the absence of pathological changes in the walls of the airways, bronchi lacking the support of a normal lung parenchyma are easily occluded: Martin and Proctor[66] demonstrated in dogs that excised segments of bronchi 2 mm in diameter were 90% collapsed by a pressure of 7.5 Cm. saline.) Such a theory would explain the excellent correlation which exists between the FEV 1.0 and measures of expiratory resistance.

By way of contrast the asthmatic person who is otherwise in reasonable health can maintain adequate ventilatory function provided he is able to compensate for his physiological defect by generating increased respiratory pressure gradients to overcome the added resistance to air-flow; and in this situation the elastic properties of the lung parenchyma become critical. If this proposition is correct it is to be expected that FEV 1.0 will correlate with lung compliance; and our present observations indicate that such, in fact, is the case. Further, the flow rate as measured by the FEV will in part be determined by the volume of air to be expelled; and it has already been noted that in asthmatic subjects the vital capacity also correlated with the lung compliance. From the present data it is therefore deduced that the elastic properties of the lung are of vital importance in determining an asthmatic's overall ventilatory performance.

Support for the contention that the diseases of asthma and emphysema differ fundamentally in their pathophysiology comes from two additional sources. Post mortem studies have demonstrated that the incidence of emphysema is no higher amongst asthmatic subjects coming to autopsy than in the population as a whole.[47,109] This is in contrast to the common clinical impression that long-standing asthmatics tend to develop irreversible morphologic changes in their lungs, producing emphysema. It is likely that irreversible changes do occur in a percentage of cases; but these are of a type calculated to produce decreased compliance[28] rather than the ultra-compliant lungs of emphysema.

Secondly, as Robin has pointed out in discussing the control of ventilation in chronic obstructive pulmonary disease,[94] patients suffering from this condition have the "choice" of maintaining adequate external ventilation at a considerable energy cost, or of conserving energy at the expense of deranged gas exchange. His views have been confirmed by a number of other workers.[87,92] The results of the present investigation suggest that it may be possible to carry this classification further, and include in the first group the vast majority of asthmatics (who rarely show derangements of blood gases[11:144]). In contrast most of the emphysematous subjects included in this study demonstrated a tendency to minimize their work of breathing by curtailing pressure, and if necessary volume exchange. In brief, asthmatic

patients work harder than do patients with emphysema because they retain the capacity to do so. If this assumption is correct it is to be expected that the asthmatic subjects as a group will tend to be larger and more muscular, and this in fact was observed to be the case.

It must be stated that while the results of this study appear to cast some light on the overall pulmonary function in asthma and emphysema, the degrees of correlation and the standard deviations as measured are not sufficient to permit in a given subject any confident predictions regarding mechanical properties of the lung based upon the values obtained by routine testing.

The negative results of this investigation are worthy of comment. In general the maximum breathing capacity failed to show a correlation with any of the parameters of mechanical lung function. It was of considerable interest, however, that in asthmatics increasing ventilatory capacity was often associated with higher airway resistances, in contrast to the emphysematous subjects. The difference between the two groups in this respect was statistically highly significant, and provided additional confirmatory evidence in support of the hypothysis now advanced regarding the relative importance of elastic and resistive properties of the lung in the two diseases.

The general failure of the maximum breathing capacity to correlate with measures of compliance, resistance and work of breathing is probably related to two factors: the many practical difficulties involved in obtaining a true value for the MBC, and the tendency towards the development of excessive pressures with resultant airway collapse during periods of rapid hyperventilation. As a result of a combination of these factors, recorded values in patients hospitalized with obstructive lung disease tend to underestimate the true maximal ventilatory capacity. There is insufficient evidence to state with certainty which of these factors predominates, but the fact that measurements made during the equally artificial forced expiratory manoeuvre still correlate meaningfully with values derived from other respiratory manouevres supports the suspician that it is the patients' understanding, cooperation and muscular power and coordination which are elements limiting the accuracy of the test.

It is obvious that the present investigation by no means exhausts the possibilities of attempting to correlate the various parameters of pulmonary function. Indeed the results which have emerged so far encourage the belief that these attempts should be extended to include further parameters as well as a search for more complex relationships. Meanwhile the tentative conclusion must be that the presently available methods for assessing lung function in the groups of patients who have been studied are complementary; and that no reliable conclusions

can be reached regarding the mechanical properties of the lungs unless formal studies of this aspect of pulmonary function are undertaken. Results to date suggest that this situation is unlikely to change while present testing methods prevail. An investigation such as the present one, however, can be expected to yield information of considerable interest regarding the fundamental pathophysiology of the disease processes which are studied.

CONCLUSIONS

It is concluded that the forced expiratory volume is the only measurement made during routine pulmonary function studies which shows a correlation with the results of pulmonary mechanics studies. In the case of emphysematous subjects, the FEV 1.0 is related to those measurements which assess resistance to airflow during expiration. For asthmatic patients the critical factor in determining airflow appears to be lung compliance.

In general it is felt that measurements of ventilometry and pulmonary mechanics studies are complementary investigations in patients with chronic obstructive lung disease.

It is further believed that emphysema and asthma represent two diseases, clinically often difficult to distinguish, which nevertheless differ profoundly in fundamental pathophysiology.

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APPENDIX I

In measuring any physiological parameter, repeated estimates will demonstrate an intrinsic variability. In addition to this, which may be termed normal variability, during the present study two additional factors tended to eompound the observed variation: the technical reliability of pressure recording obtained from the oesophagus, and the fact that the patients were in a pathological state which is believed to be characterized by increased variability in the parameters that were measured.

Previous workers[79] have set arbitrary limits in selecting breaths to be analyzed for the purpose of obtaining mean values of lung compliance and airway resistance. It was felt that in the context of the present investigation this might well convey a spurious arithmetical accuracy, valid only if the respiratory system is considered as a machine of constant efficiency; and examination of tracings obtained from patients during the study appeared to contradict this possibility.

Values for CL, Ri, and Re were therefore calculated for 10 - 20 consecutive, representative breaths taken from a segment of the record where the tidal volume remained constant. These were unselected save for the elimination of any which showed obvious artefacts of the pressure tracing, such as may result from superimposed cardiac impulses or temporary increases in intrinsic esophageal tone.

At the conclusion of the investigation a specimen record (obtained from Subject I in the asthmatic group, who showed greater variability from breath to breath than may of the subjects) was analyzed in detail, to confirm that the mean value employed for comparison was in fact representative of a single population. The results of this analysis are appended.

Values Obtained From Analysis of 20 Consecutive breaths:

	CL	Ri	Re
	.042	5.69	14.96
	.040	7.93	12.21
	.035	9.02	14.53
	.035	6.82	13.22
	.040	9.38	10.99
	.035	9.68	12.85
	.039	6.51	13.60
	.037	5.94	12.98
	.044	7.16	11.94
	.040	8.64	11.51
	.040	8.64	11.51
	.040	8.13	13.11
	.040	7.67	11.13
	.038	9.19	9.49
	.038	7.00	12.32
	.029	6.79	13.39
	.040	8.40	11.96
	.039	7.47	15.55
	.038	5.78	12.87
	.040	6.93	10.10
	.038	7.97	11.51
Mean	.03835	7.61	12.51
S.D.	.0032	1.117	1.5
S.E.	.007	.2504	.3355

APPENDIX I

The readings were divided into two groups of ten observations each, by random selection. The standard error of the difference and the relative deviate were calculated for each value, which was tested for uniformity of population by the null hypothysis:

CL: Group I mean value .0386

Group II mean value .0381

$S.E._{Diff.}$ .0137

Relative Deviate $\frac{.0386 - .0381}{.0137} = .0364 \quad p > .9$

Ri: Group I mean value 7.627

Group II mean value 7.583

$S.E._{Diff.}$ .524

Relative Deviate $\frac{7.627 - 7.583}{.524} = .084 \quad p > .9$

Re: Group I mean value 12.76

Group II mean value 12.25

$S.E._{Diff.}$ .657

Relative Deviate $\frac{.51}{.657} = .776 \quad p > .4$

It was therefore concluded that the mean values obtained by this method of analyzing the tracings were representative of a single population.

APPENDIX II

Measurement of Work Loops

Work loops were constructed in the usual way from records of intraoesophageal pressure and tidal volume. Measurements were facilitated by the use of the E for M Oscilloscope Recorder type DR-8. Using time lines at 0.04 sec. intervals, each breath was sub-divided into a minimum of 30 segments for analysis and measurement.

It had originally been intended to draw the loops on graph paper ruled off in one-centimetre squares, and to measure the area by planimeter. During the course of the study it was found that the planimeter readings were unreliable. The work loops were therefore drawn on good quality paper of standard weight (K and E graph paper # 48 5123) and the various fractions of the loops measured by cutting them out with scrupulous care and weighing them on a scale which measured to .001 Gm. (Gram-atic Balance, Fisher Scientific Co.).

This method was found to give satisfactory and reproducible results.

APPENDIX III

EXPERIMENTAL ACCURACY

a) Measurement of Lung Volumes:

The accuracy of this procedure was assessed by making repeated measurements at 20 minute intervals on a 36 year old non-smoker. The results were as follows:

	V.C.	F.R.C.
	4.13 litres	3.00 litres
	4.06 litres	2.96 litres
	4.06 litres	2.96 litres
% variation	1.7	1.3

b) Measurement of Pulmonary Mechanics:

Repeated estimates of lung compliance and airway resistance were made at 30 minute intervals in a 21 year old non-smoker with the following results:

CL	Ri	Re
.237	1.26	1.89
.246	1.49	1.86
.252	1.27	1.63

The observed variation, which is in the range of 10% or less, is believed to be due to a combination of normal variability and technical errors inherent in the method of recording pressures.

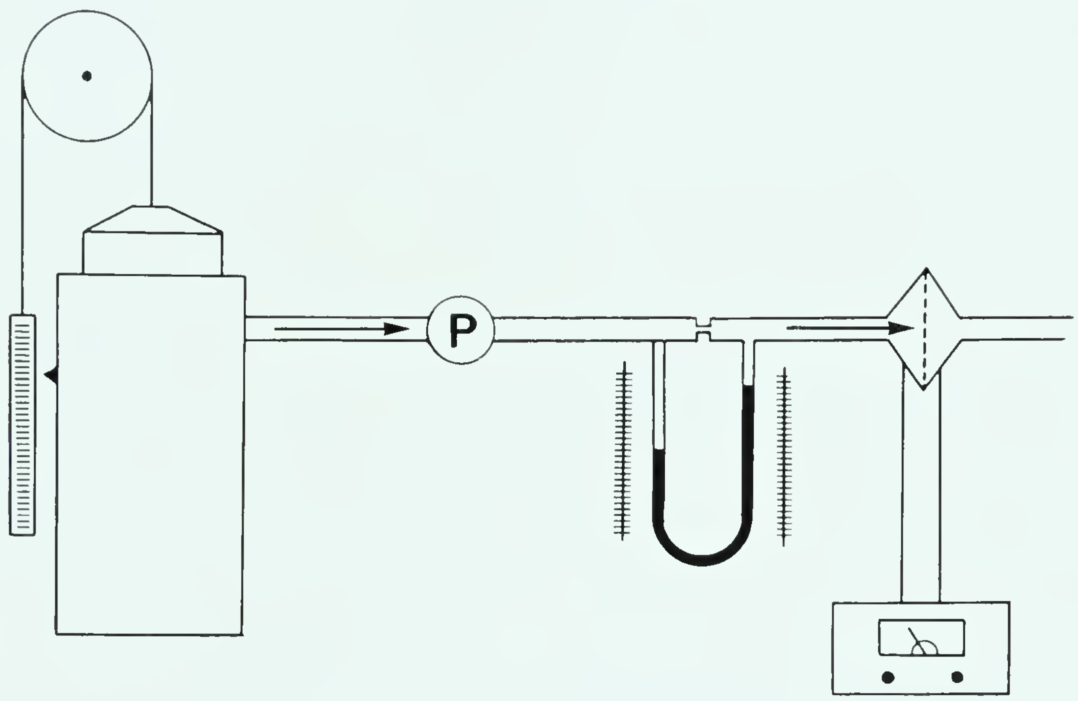
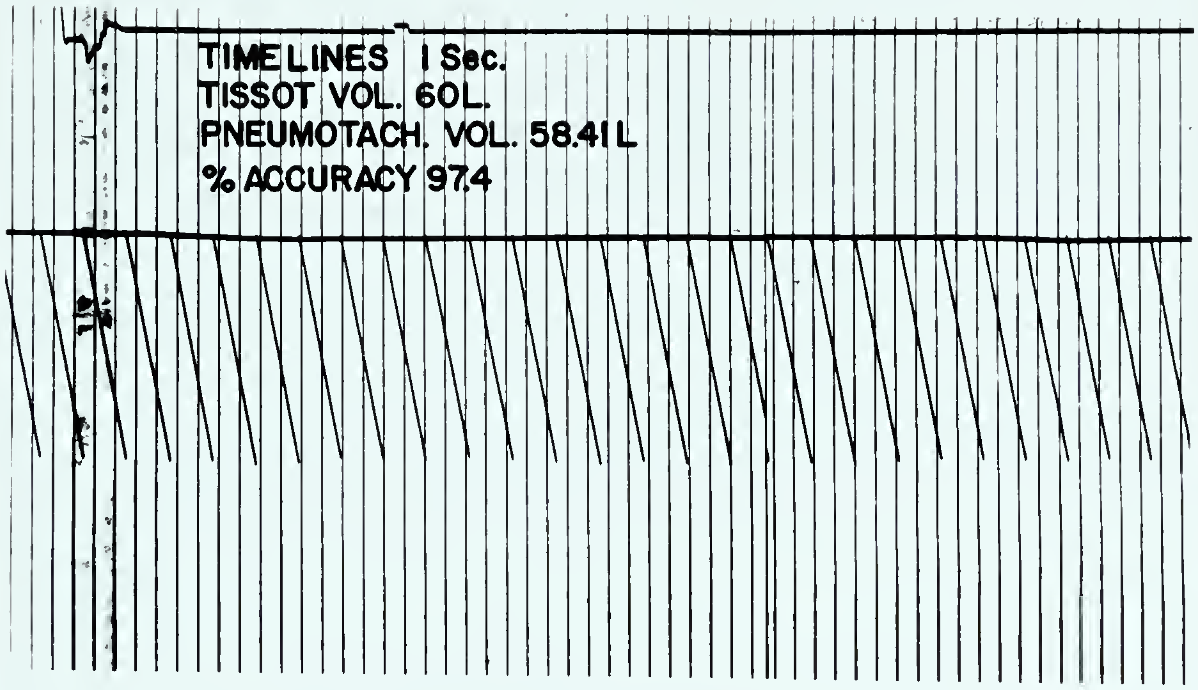


Figure XV

Diagram of Calibration Method: See Text.

Figure
XVI - A



Calibration Strips

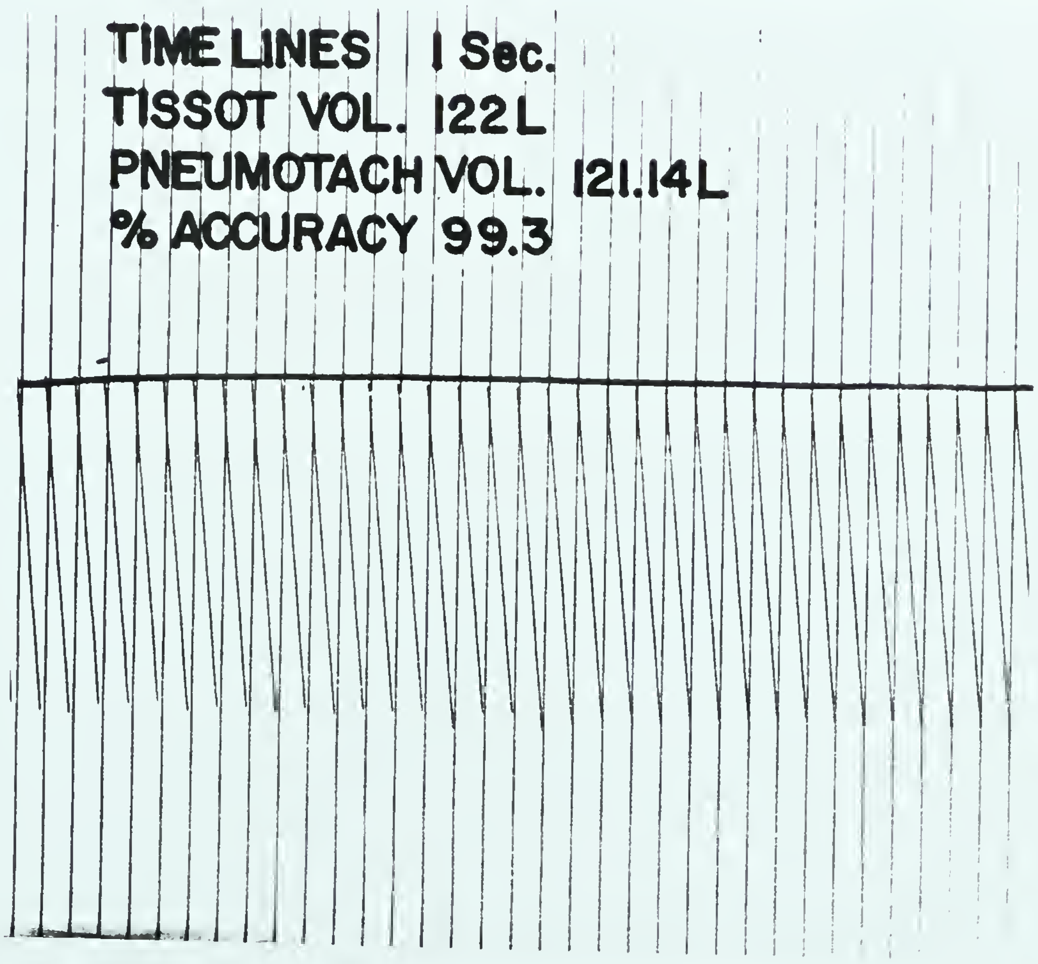


Figure XVI-B
Note: Figures refer to minute volumes.

APPENDIX IV

CALIBRATION OF PNEUMOTACHOMETER

a) Flow:

The pneumotachometer was calibrated with the Godart flow meter type 121 and found to be linear for flow rates up to 130 litres per minute.

b) Volume:

The accuracy of the volume calibration was estimated according to the method outlined diagrammatically in Figure XV. A known volume of gas, measured in a Tissot spirometer (120 litres Collins Gasometer) was pumped at a known flow rate into the pneumotachometer, and the recorded volume measured. (The calibration strips obtained are presented in Figure XVI.) The results were as follows:

Tissot Volume	Flow Rate	Pneumotach. Volume	Time	% Accuracy
60 L	60 L/min.	58.41 L	60 secs.	97.4
61 L	122 L/min.	60.57 L	30 secs.	99.3

ABBREVIATIONS

VC	vital capacity
TLC	total lung capacity
RV	residual volume
FRC	functional residual capacity
V_T	tidal volume
FEV (0.5, 1.0)	forced expiratory volume (0.5, 1.0 seconds)
MBC	maximum breathing capacity
MMEF	maximum mid-expiratory flowrate
CL	lung compliance
Ri	inspiratory airway resistance
Re	expiratory airway resistance
$\bar{R}$	mean airway resistance
r	coefficient of correlation

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